SER. II. VOL. 19 NO. 5

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SER. II, VOL. 19 *March 1957* NO. 5

TRANSACTIONS
OF
THE NEW YORK ACADEMY OF SCIENCES

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Contents

Some Geological Processes at Work on Coral Atolls. *By* F. R. FOSBERG 411
On the Theory of Oxidation-Reduction Reactions and of Related Processes. *By* R. A. MARCUS 423
Criteria of Malignancy:
I. Morphology of Detroit Strains of Human Cells in Tissue Culture. *By* LAWRENCE BERMAN, CYRIL S. STULBERG, AND FRANK H. RUDDLE 432
II. Biological Consideration of Normal and Abnormal Cell Lines. *By* ALICE E. MOORE 435
Present Knowledge of Nystatin, an Antifungal Antibiotic. *By* RACHEL BROWN AND ELIZABETH L. HAZEN 447
Psychoanalysis as Anthropological Field Work: Data and Theoretical Implications. *By* GEORGE DEVEREUX 457
Conference Held 473
New Members 477

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Transactions of The New York Academy of Sciences, Series II, Volume 19, No. 5, March 1957.

Entered as second-class matter December 28, 1954, at the post office at New York, N. Y., under the act of August 24, 1912. This publication is distributed to members and is published monthly from November to June, inclusive, by The New York Academy of Sciences, 2 East Sixty-third Street, New York 21, N. Y.

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SECTION OF GEOLOGY AND MINERALOGY

SOME GEOLOGICAL PROCESSES AT WORK ON CORAL ATOLLS*

By F. R. Fosberg

United States Geological Survey, Washington, D. C.

Coral atolls are flat islands or groups of islands composed of limestone of organic origin lying on limestone reefs that are usually somewhat ring-shaped. They enclose bodies of relatively shallow water called lagoons. Generally coral atolls reach only 2 or 3 m. above sea level, except where winds have piled sand into dunes, or where storm waves have piled up ridges of gravel or boulders. Occasional atolls are emerged, even to a height of over 100 m.; some are submerged and consist of only a ring-shaped reef with no dry land. Atolls are distributed through the tropical seas of the world, but are most common in the central and western Pacific and western Indian oceans. They are almost nonexistent in the eastern Pacific, and completely absent in the eastern Atlantic.

The origin of these structures – reefs plus islands – is generally associated with a differential movement of sea level and substratum when the substratum subsides in relation to the surface of the sea. This generalization, first stated by Charles Darwin,[1] has in very recent years been shown, with scarcely any doubt, to be sound, at least for most atolls,[2,3] but there still remain many questions concerning atolls that are not completely resolved. Not the least of these deals with the origin of the islets that emerge above the sea.

Darwin believed that the differential movement referred to above resulted from regional subsidence of the sea bottom. Since his time it has been shown that general or eustatic changes of sea level have taken place at least during periods of alternating glaciation and melting. More extreme shifts have been suggested, but they have not been proved. Tectonic movements of more restricted areas of the sea floor have clearly occurred, and isostatic settling of single volcanic mountains standing above the sea bottom is almost certain, although this is not universally accepted as a fact. In most parts of the coral seas at least the widespread regional subsidence suggested by Darwin is now regarded as unlikely.

The origin of the entire atoll structures is a subject that has received a great deal of attention from great geologists, and several very adequate discussions and summaries of their ideas are available.[4-9,15] Some of the more restricted processes at work, particularly on atoll islets and reef surfaces, have been less adequately studied. These processes,

*This paper, illustrated with lantern slides, was presented at a meeting of the Section on February 4, 1957.

The publication of this article has been authorized by the Director, United States Geological Survey, Washington, D. C.

perhaps, present more local variation, and they will be the principal subject of this short discussion. Incidental to my other work, I have had the good fortune to see and study some of these processes and their results in such widely separated areas as the Micronesian atolls, especially the Marshall Islands, the Central Pacific atolls, the Tuamotu Archipelago, and the Maldive Islands, where the word atoll originated. This account will be a brief outline of the more obvious processes, filled in more fully by pertinent observations made or verified during actual work in the field. The short bibliography appended will enable those interested to obtain more detail, both on the local processes and on the theories of atoll origin.

It is necessary briefly to describe the general profile and surface features of atoll reefs in order to locate and understand the processes discussed below. The slopes of the submarine mountains that are topped by atoll reefs rise in long ever-steepening curves from the sea bottom to very near sea level, where they may even become vertical. The margin of the reef is often deeply scalloped or toothed and cut by chasms called surge channels through which the waves rush and retreat. Algal growth on the edge of these channels is relatively rapid and tends to roof them over. In general, on windward sides of atolls, rapid growth of massive calcareous red algae extends the reefs outward and upward. Storm waves pluck off unstable extensions outward, and overexposure to air limits upward growth. However, a windward margin tends to be elevated in the form of a low ridge of hard, pink living algae within the limit below which the waves keep the surface continuously wet. The ridge is cut by surge channels, and back of it is usually found a shallow depression or trough. From this ridge, or on leeward sides, from the reef margin, a plane surface, often fairly smooth, slopes very gently upward, averaging about low tide level. This is called the reef flat. Between islets it rises to a half meter or so above mean low tide, then slopes as gently down to the inner edge of the reef and lagoon. This flat is cut by shallow cross channels and deeper passes and gaps. Where there are islets the reef flat rises either to the lower edge of the beach or to a more steeply sloping, usually rough rock surface called the erosion ramp. This ramp extends up to high tide level where it may end in a low ledge of rock or in the lower edge of a storm beach. Where present, the ledge of rock, usually a coral conglomerate, is probably composed of the remnants of a higher reef surface, formed during a period of postglacial warm climate when the sea level was about 2 (or 3.5) m. higher than at present. This rock is called the platform, and may extend under the loose sediments of the islet partially or totally to the lagoon shore. The islets may be partly outlined by linear, somewhat dipping beds of consolidated material called beachrock. The loose surface of the islets is generally of very low relief, but the peripheries, especially on the sea-

ward sides, may be elevated into low beach ridges of sand, gravel, cobbles, or boulders. On some islets there are parallel ridges, separated by shallow troughs. The lagoon is generally somewhat basin-shaped, seldom more than 80 m. deep. The bottom is usually very irregular, at least locally, with knolls, pinnacles, patches of reef, and large individual corals forming knobs or branching like trees.

The processes discussed may be classified roughly into constructive, stabilizing, and destructive categories, and some of the results of these processes may be expressed in terms of origin, migration, and destruction of islets. It must not be supposed, however, that these processes actually separate themselves so neatly. As with most natural phenomena, sharp separation into categories, or even into processes, is usually the result of the efforts of the human classifier to deal with and understand very complex situations. All of these processes are in operation simultaneously and the structures that result from their combined actions have the nature of dynamic equilibria rather than of static phenomena.

Constructive processes. The basic constructive process is, of course, the production of calcium carbonate minerals by organic means. Many animals and plants secrete limy skeletons, usually composed of either calcite or aragonite. This is an especially common and conspicuous process in warm shallow waters in the tropics. The physiology and chemistry of this process are not well understood, but active investigation of it is being conducted in the Bermuda Biological Station. Some of the more important groups of organisms that contribute in this way to the growth of reefs and islands are, among the animals, corals and other coelenterates, Foraminifera, mollusks, and echinoderms and, among plants, calcareous red and green algae. Between corals, Foraminifera, and algae it would be difficult to generalize as to which contribute the most lime, but the total quantities are enormous. On Eniwetok Atoll, borings have revealed that the thickness of this type of limestone is between 4000 and 5000 feet. It is possible roughly to localize the areas of greatest activity of these different lime producers, but any quantitative statements either as to rate or amount of production are at this stage likely to indicate only orders of magnitude, and they are valid only for the time and precise location where the observations were made. It seems probable that agitated, thoroughly aerated water is conducive to the greatest growth, but even this may be questioned. It does seem certain that production is greatest in the upper layers of water where light is abundant.

Reef growth takes place where a sufficient abundance of attached lime-secreting organisms are growing under such favorable conditions as to produce aggregations of limy skeletons sufficiently massive to form a rigid lattice or framework. This framework tends to be bound together and strengthened by the growth of encrusting limy organisms and to col-

lect and hold loose fragments and the free tests of Foraminifera. It is a point of argument whether the term reef should be applied only to the lattice or to the entire accumulation, but the latter application seems more sensible.

Sedimentation of several different types is an obvious and fundamental process in the building of reefs and islets. It is a process that may be considered to include any form of deposition of lime (or other solid material) other than the actual growth of the calcareous skeletons of organisms. In the reef interstices there is a steady accumulation and filling in by fragments detached from the sessile organisms and by loose skeletons of the free-living ones. On the reef surfaces large blocks and rubble tracts are deposited by storm waves that may break off fragments, often of enormous size, from the reef margins and other features undergoing erosion, or that may pick up and redeposit material already in loose form. Masses of gravel and sand may also be moved and redeposited by storm waves. A more constant but less spectacular process is the deposit of sand- and gravel-sized material in the form of bars, spits, horns, and lobes on the reef flats by ordinary waves and tidal currents. The basic process here seems to be the carrying of material across the reefs by waves and currents running from the sea toward the lagoon, to be dropped when the energy of the waves has been spent or is neutralized by smaller counterwaves from the lagoon. For this reason bars are more frequent on wide than on narrow reefs. A contributory factor is the larger amount of fine material supplied by the wider reefs. A very curious phenomenon is the formation of sand horns at the inner corners of islets on wide reefs. These horns are elongate spits that mark the boundaries of influence of ocean and lagoon waves. With seasonal changes in the relative strength of these two types of waves, these narrow ridges change their positions, extending toward the lagoon in periods of strong and constant sea wave action and lying parallel with the reef in times when the lagoon waves are relatively stronger. The effect can be imagined as a slow flapping of wings or as a waving of tentacles extending from the islets. When these spits are relatively short and wide they are termed sand lobes. Such horns and lobes are developed most notably in connection with islets on windward reefs in the trade-wind belts.

On the reef flats there is a tendency for any irregularity to accumulate loose sediments. This is especially true of rubble tracts or aggregations of larger blocks on the reef. Here the interference of the larger masses tends to dissipate the energy of the waves, causing the deposit of large amounts of loose material and its accumulation to form bars and islets.

Both wind and waves drop material on dry land areas. The waves, particularly storm waves, deposit material ranging from fine sand to boulders to form ridges paralleling the shores, and also to form beaches sloping

down to the rock foundation on which the material is laid. Typhoon waves also scatter great blocks and boulders inland for as much as hundreds of meters, leaving them as sporadic boulders or as block fields. Winds lift the finer material from the beaches and blow it across the land surfaces. Small dunes may be formed due to configuration of land alone, but they are far more likely to be the results of interference and dissipation of wind energy by vegetation. Dunes are most frequently seen on the edges of forests and around clumps of bushes or trees. Even grass may collect some sand. Wave- and wind-deposited material cannot be easily separated and it may be closely interbedded in places. Beds with significant amounts of gravel or larger fragments are in all likelihood wave-deposited. In addition to depositing sand on land in the form of ridges, layers, and dunes, the wind may carry some fine material to the lagoon shore or into the lagoon itself.

In the lagoon sedimentation is a constant process. Waves carry clastic material of all sizes across the reefs and pour it into the lagoons. Typhoon waves may strip great quantities of loose material from the land and fill the adjacent parts of the lagoon, as must have been the case on Utirik Atoll. Studies on Bikini by Ladd and his associates (1950)[2] show that there is a constant migration of fine sediments, largely foraminiferal tests, from the windward reef flats around the islets, along the beaches, and into the lagoon. Calcareous material is also being produced in the lagoons by green algae *(Halimeda)*, corals, Foraminifera, mollusks, and other organisms. This may be deposited either as reefs or as sediments. Recent studies (Emery, 1948,[11] McKee, verbal communication) have shown that on lagoon bottoms there is a definite zonation of sediments by depth according to the organisms contributing most abundantly to the sediments. The thing that is difficult to understand about lagoon sedimentation is why lagoons do not fill up much more rapidly than they appear to do.

A final type of sedimentation, one about which less is known, is the constant deposition on the outer submarine slopes of material of all sizes from silt to enormous boulders and collapsed sections of reef. Large boulders can be seen on the upper parts of the slopes or are encountered in dredging and sounding. Gravel and cobbles are commonly seen in the bottoms of surge channels. At the outer ends of channels and other openings through reefs the water is sometimes seen to be somewhat milky in appearance, indicating that a certain amount of silt is being carried out from the lagoon to be deposited outside.

Stabilizing processes. These are closely involved with the processes here termed constructive. They can be divided into those producing relatively permanent results and those of a more temporary nature. We have referred to the bonding of reef edges and surfaces and the cementing together of loose material and components of the growth lattice by limy

encrusting organisms, both algae and animals. Occasionally smooth algal pavements result from these processes, and the reefs are immeasurably strengthened against the pounding of waves. Cementation of loose clastic material into reef conglomerate is a process that has been little investigated and is not understood. It probably takes place between tide levels, but even the nature of the calcareous cement does not seem to be known, let alone the circumstances of its deposition. Beachrock cementation, on the other hand, has been studied intensively. It is known that the bonding material may be a fine-grained calcite matrix or an encrustation of needlelike crystals of either aragonite or calcite; that initial cementation may take place between tides in the interior of beach deposits; that the rock, when first formed, is not very well indurated; that it is firmest toward the top and softer and more easily crumbled toward low tide level; and that cementation is a relatively rapid process. Apparently nothing is really known of the conditions under which this cementation takes place or fails to take place, although many theories concerning it have appeared.[12, 13]

When any of these reef limestones is exposed to air there occurs a phenomenon that has been called casehardening, the exact nature of which is also poorly understood. A recrystallization of the limy material must be involved. The outer layers of rock become very firmly indurated and the material becomes increasingly resistant to most forms of erosion. It is probable that if it were not for this surficial hardening beachrock would be a very short-lived material. The conspicuous exposures of beachrock that extend above high tide level around so many atoll islets were, in all likelihood, formed when the sea stood somewhat higher than it does at present, and have been preserved by becoming casehardened.

A recently elucidated phenomenon is the formation of bedded atoll phosphate rock, or hardpan. This is thought to occur only in forests of a common atoll tree, *Pisonia grandis*, in which a large number of sea birds roost and nest. The humus accumulating under these trees is very acid, *p*H 4.5 to 6, and decomposes much more slowly than is common in the lowland tropics. Layers up to 10 to 20 cm. thick form on the surface of the loose calcareous sediments. Bird guano, at *p*H 6 to 7, falling from the trees above onto the surface of this humus is washed into it by rain water. Being acidified by the humus, the solid finely divided phosphate material goes into solution and percolates downward until it enters the loose limestone material beneath. Here it precipitates out, cementing the particles of sediment together with a brown phosphate cement. With continued exposure to this slightly acid solution of phosphate, the calcium carbonate is gradually but at length completely replaced by calcium phosphate to form the characteristic beds of phosphate rock that were formerly widely collected from coral atolls and sold for fertilizer as "guano."[14]

There are several much more temporary stabilizing processes. On the reef surfaces fine furs or felts of filamentous algae collect and hold silt and even fine sand. Pinkish masses of the genus *Schizothrix* hold fine silt in a putty-like form on reef flats, erosion ramps, and very shallow lagoon margins. On land loose sand surfaces are held in a crust by other microscopic gelatinous blue-green algae. This crust is soft when wet and friable when dry. In addition to stabilizing the surface, these algae may also encourage the growth of higher vegetation by providing a source of fixed nitrogen, although this is not yet fully demonstrated. Mosses also spread over the surface of sand in shady places and hold it down. Without the binding effect of the roots and the protective effect of the shoots of higher vegetation, the loose sediments composing the bulk of the islets would be shifted and moved to some extent by every wind or wave that touched them. When covered by vegetation an atoll islet becomes a relatively more permanent structure and a fit spot for colonization by man and other land animals.

Destructive processes. The destructive processes are many. Judging by the abundance of its products, one of the most important is wave erosion on the outer margins and upper slopes of reefs. The enormous quantities of huge coral and algal blocks and boulders, individual corals, and colonies of algae that are scattered on the reef flats and piled in ridges along the outer edges of islets show that the tearing loose of masses of limestone by storm waves is a very active process indeed. It is evidently effective down to some depth on the outer slope, judging by the large size of some of the coral colonies thrown up, but how far down is not known. This process is doubtless extended by a tendency for reefs to grow outward until they overhang to a point of instability.

The rounding of particles, from boulders down to individual foraminiferal tests, is also shown by its effects to be a widespread and constant process, although details of how it operates are for the most part inferential. Rolling of these particles back and forth over reefs by waves and tidal currents is the obvious general mechanism of rounding. MacNeil's observations on beach sands (unpublished) showed that the particles on the windward sides of windward islets on the northern Marshall Atolls are very little rounded, but that, as samples come from nearer the leeward reef, the rounding is more pronounced, and on the leeward sides of leeward islets the particles are strongly rounded. These facts accord with observations made by Ladd and his associates[2] (1950) indicating that much of the beach material is produced on the windward sides of islands and migrates around toward the lee sides.

A conspicuous feature of reef flats for which, so far, there has been offered no satisfactory explanation is the common occurrence of long straight or curved cracks tens to hundreds of meters long with no regular orientation. Whether these cracks are due to a settling or compaction of

the reef, to strains from tectonic causes, to chemical changes producing differences in volume, or to some unsuspected cause is not known.

A considerable amount of living coral is reduced to sediment by the action of coral-feeding fish, especially parrot fish, that abound in the neighborhood of reefs. These fish have elaborate grinding mechanisms as well as hard sharp jaws with which they bite off and pulverize pieces of coral from which they extract organic matter for their nourishment. They excrete the ground-up limestone of the skeletons.

Typhoon waves at times remove vast quantities of loose sediments from reefs, an action that contrasts with their constructive activities. Whole islets have been washed away in a single storm. Channels have been cut through narrow islets. Beach erosion is in places conspicuous. Sand islets in and around the lagoon of Malé Atoll, Maldive Islands, all seemed to be undergoing active cutting away, undermining coconut trees and other vegetation. By nature, however, beaches are very transient structures.

Large boulders lying either on the reef or on land are frequently observed to be fragmented into smaller pieces. The cause of this fragmentation has not been determined, although roots of plants may at times be responsible. Terrestrial sediments of all size classes are, of course, continuously subject to a certain amount of solution by rain water. The results of this process would be difficult to measure, but the aggregate of limestone removed in this way must be enormous. Boring algae, mostly or entirely Cyanophyceae, are present in all exposed surfaces of coral limestone. They soften the surface and tend to accelerate solution. Nesteroff (1956)[16] places the microscopic algae first among the agents of both intertidal and supratidal erosion.

The complex of processes of intertidal erosion resulting in planation of reefs is of enormous importance in determining the coral atoll landscape. If one is correct in the assumption that, during the postglacial high-sea level in the climatic optimum, reefs grew up to either 2 or 3.5 m. above the present low-tide level, then the entire expanse of present-day reef flat near mean low-tide level has been planed down to this height in the several thousand years since the start of the eustatic fall to the present sea level. The areas of most active intertidal erosion at present seem to be the nips that surround boulders and erosion remnants lying on the reefs and the rough sloping surface rising from the reef flat around islets that has been termed the erosion ramp. These two features are between low- and high-tide levels and, when studied carefully, they show signs of several distinct erosional processes. An obvious one is solution. Solution pits of all sizes are very apparent on the ramp surfaces. The large ones have characteristic vertical sides or overhanging edges and flat bottoms. What seems to be precipitated chalk may be seen in some of the pits that are at higher levels on the erosion ramps. Rain water or

sea water diluted by rain water may be important in producing these pits, but it is probable that changes in temperature, as well as the production of CO_2 by organisms, may make possible some solution by sea water, even though the latter is commonly regarded as saturated or even supersaturated with $CaCO_3$.

A number of features attributable to abrasion are frequent on erosion ramps as well as in nips. Where abraded, erosion surfaces that normally have a very sharp microrelief have rounded bumps rather than points. Surfaces normally darkened by boring algae are white or pale gray where abraded. On erosion ramps, basins and potholes are frequently developed where pebbles become lodged in pits or irregularities. On fairly steep ramps these depressions tend to elongate in a direction perpendicular to the shore and to coalesce to form grooves. On many ramps conspicuous parallel channels run down the slope, probably of this same origin, but worn very smooth and regular by the constant rolling of pebbles by waves. These are very well developed on Jemo Island and have been illustrated in plate I of the work by Schlanger and Brookhart (1955)[17] for Ulithi Atoll.

Spalling, the "exfoliation" of Newell,[7] is the breaking off of horizontal slabs from the ramp surface. It was observed to be very common in the northern Marshalls and to leave conspicuous flat surfaces. It is presumably caused by the sudden cooling by the rising tide of rock heated by the sun. The slabs vary from a few centimeters to almost a meter across.

Undercutting and collapse constitute locally a conspicuous process where the sea attacks weaker, more poorly cemented beds underlying stronger ones, undermining and causing eventual collapse of the upper beds. Much of the large rubble found lying in tracts on reef flats may have this origin. In places, as on the north shore of Wotho Islet, this process is conspicuous and has resulted in the removal of at least two layers of reef rock. It is possible that strong waves may vary this process by actually forcing up the upper layers after openings have been hollowed out beneath them.

Although it can scarcely be measured, the destructive action of the organisms dwelling in the intertidal zone may actually make the most important contribution to reef planation. This action has been and is being studied by many workers (for example, Bertram[18]). Indirect influences such as increased solution because of CO_2 production have been suggested, and attempts have been made to measure the effects. Direct effects may result from boring, rasping, or grinding. Among the known marine borers affecting intertidal limestone are algae, sponges, mollusks, cirripeds, and sipunculids. Certain intertidal layers of limestone on erosion ramps in the Marshalls were observed to be actually riddled by burrows inhabited by sipunculids. It is not known how these organisms make their burrows, as they have no mouth parts capable of such action. It is possible

that they secrete acids that dissolve the limestone. Some gastropods feed by rasping algae from the surface of the rock with their radulae. Echinoids are known to grind pits in intertidal rock and, at least on Bikar Atoll, one species, *Heterocentron trigonarius*, appeared to be responsible for, or at least associated in large numbers with, conspicuous erosion features in the algal limestone at the reef margin. Holothurians in tide pools on reefs ingest quantities of lime sand, but it is not known just how much effect they may have in grinding or dissolving it.

Islet formation. Islets seem to originate in several ways, resulting from different combinations of all of the categories of processes listed above. Little is known of their origin from direct observation except about stages in the processes. For the most part the origin of these islets must be inferred from examination of their characteristics and by attempting to derive these features from the action of observed processes.

Most islets seem to be erosion remnants of higher reef platforms left by a fall of sea level following the postglacial climatic optimum and associated loose sediments. In this type of islet, remnants of the platform are usually exposed, often extensively, on the seaward side. The platform surface lies at or above present high-tide level. It extends lagoonward under the loose sediments and vegetation for varying distances, rarely reaching completely across the islet and showing on the lagoon side. At least on a given atoll the remnants of this platform are usually of about the same height except where they are obviously eroded locally. At least in the northern Marshalls, such islets are most plentiful on the windward reefs, less so on the south reefs, and rare or absent on the west reefs.

Another type of islet evidently forms by the accumulation of loose sediments around tracts of large storm-tossed rubble on the reef flat and their subsequent stabilization by vegetation or by the formation of beachrock. This type is hard to recognize with certainty, except during the course of formation or destruction, because the rubble tends to be completely buried by smaller sediments.

Still another type of islet starts as an accumulation of sand or gravel in the form of a bar on a wide reef flat. With stabilization, again either by vegetation or by the formation of beachrock, additional material tends to accumulate, causing growth of the islet.

A fourth type results from the deposition of loose materials in the lagoons near the inner ends of channels or in passes through the reefs. This process is not yet well understood, but it occurs frequently enough to indicate that a definite principle is involved. The origin of occasional sandy islets within lagoons at a considerable distance from any channel or passage through the reefs likewise is not understood. Such islets were observed more commonly in Malé Atoll, Maldives, than elsewhere.

Logically, one would expect rocky islets to be common in lagoons if patch reefs were as common in climatic optimum lagoons as they are now, but they are seldom seen. One such islet was observed in the lagoon of Maria Atoll in the Austral group.

Migration of islets. One final phenomenon must be mentioned, the apparent migration of islets across the reef that has been pointed out by many students of atolls. This seems to occur where there are strong prevailing winds from one direction. The windward side of the islet is usually rocky, generally with an exposed platform remnant. The leeward side is sandy. There seems little doubt that such migration results when constructive processes predominate on the leeward side and destructive ones predominate on the windward. Since many of the destructive processes are associated with strong wave action, since finer materials may be removed by wind as they are formed, and since deposition occurs especially on or toward the leeward, this migration would be expected. In addition, we know of many cases in which the destructive processes have predominated and islets have disappeared, leaving their outlines in beachrock remnants. There remains the logical question of how much time will elapse before the planation processes will have done their work completely, leaving the reef flats bare except for the occasional or at least less numerous islets of the two purely depositional types that occur there.

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SECTION OF PHYSICS AND CHEMISTRY

ON THE THEORY OF OXIDATION-REDUCTION REACTIONS AND OF RELATED PROCESSES*

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Recent years have witnessed the elucidation of the mechanisms of many organic and inorganic chemical reactions. Several principal factors have contributed to this development. Among these may be listed the detailed kinetic study of numerous reactions, and the use of isotopic tracers, in some cases, to map the migration of specific atoms between the reacting molecules. Another factor is the deep insight into reaction mechanisms afforded by qualitative application of the ideas of modern valence theory, such as those embodied in the conception of the activated complex.

Oxidation-reduction reactions provide typical examples of this trend. Detailed kinetic studies have shown that they frequently involve a number of successive reaction steps. Attention has become focused on the rates and mechanisms of these elementary reactions, some of which are equilibria involving the formation, or disappearance, of the species participating in the actual redox step.

Similar remarks apply to electrode processes, whose slow rate is one cause of overvoltage and of polarographic irreversibility. Detailed studies of the mechanism of these processes, frequently by alternating current techniques, are comparatively fewer, but they have begun to reveal the complexities and trends involved.[1-6] These processes, too, may involve several successive steps, some of which are associated with the formation or disappearance of the reacting particle undergoing electron or atom transfer with the electrode. Isotopic tracer techniques have been employed here also.

Tentatively, one may draw from the studies of redox processes several generalizations that are especially pertinent to the ensuing discussion:

(1) In a homogeneous oxidation of a series of chemically related compounds differing only in some substituent, some correlation usually exists between differences in over-all reaction rate and differences in the standard free energy change of the reaction.[7]

(2) The study of reactions having zero standard free energy change permits a closer evaluation of other factors affecting the reaction rate. Excellent examples of such processes are isotopic exchange reactions[8]

*This paper, illustrated with lantern slides, was presented at a meeting of the Section on February 5, 1957.

The research described in this paper was supported in part by the Office of Naval Research under Contract No. Nonr 839(09). Reproduction in whole or in part is permitted for any purpose by the United States government.

between ions differing only in their valence state, such as those in EQUATIONS 1 and 2:

$$Fe(H_2O)_6^{*+2} + Fe(H_2O)_6^{+3} = Fe(H_2O)_6^{*+3} + Fe(H_2O)_6^{+2} \quad (1)$$

$$Fe(CN)_6^{*-4} + Fe(CN)_6^{-3} = Fe(CN)_6^{*-3} + Fe(CN)_6^{-4} \quad (2)$$

(The asterisk in these equations denotes a radioactive ion.) It appears from these studies that ionic size, Coulombic repulsion, and differences in corresponding interatomic distances in the two reactants affect the reaction rate.

(3) Some parallelism appears to exist between the rate at which a material undergoes electrolysis at a given overvoltage and the rate at which it undergoes an isotopic exchange redox reaction. For example, the rate of the isotopic exchange reaction between small hydrated cations is smaller than that between the complex iron cyanide ions.[9-11] Correspondingly, the former form systems less reversible electrochemically.[12] Similarly, the isotopic exchange reaction between the cobalt ammines is slower than that between cobalt ethylenediamines[13] and, again, the former form electrochemically less reversible systems.[14,15]

The mechanism of the actual redox step in a process may be one of electron or atom transfer between the reactants. Generally the reaction kinetics alone cannot distinguish between these two paths. Isotopic tracers have established an atom transfer mechanism in several cases,[16,17] but their use is limited to reactions in which no alternative nonredox path is available for the transfer. For example, the method is inapplicable if the atom, such as the phenolic hydrogen in hydroquinones, is highly labile.

Nevertheless, several approaches based on recent theoretical developments can be tentatively suggested for distinguishing between these two mechanisms in such cases. These will be considered later.

We shall first examine a possible electron transfer mechanism and some of its consequences.

In 1952 Libby[18] applied the Franck-Condon principle to isotopic exchange electron transfer reactions, pointing out that the atoms did not have time to move during the rapid electronic jump. This line of reasoning focused attention on the role played by the co-ordination shells and hydration atmospheres of the two reactants. The more similar the two reactants were in this respect, the less would be the energy barrier to reaction. These ideas were explored in more detail by the present writer, who later formulated a quantitative theory for electron transfer processes. The results of this investigation are outlined in the succeeding paragraphs.

In most chemical reactions, bonds are formed and broken in the critical collision, or activated, complex, and this will generally require a large interaction of the electronic structures of the two reactants. In contrast,

only a weak electronic interaction of the reacting molecules may be necessary to couple the reactants electronically and so permit an electron transfer process to occur.

Assuming that these electronic orbitals interact but slightly in the activated complex, I have shown[19] that the latter proceeds through two successive states. These have the same energy and the same atomic configuration, but the first has the electronic configuration of the reactants, and the second has that of the products. This restriction of constant energy is far-reaching and does not obtain in reactions having a large interaction of the orbitals of the two reactants. In those reactions, the electronic configuration of the critical collision complex can sometimes be approximately regarded as consisting of a "quantum mechanical resonance" between two strongly interacting electronic structures (that of the reactants and that of the products). These two resonance structures have the same atomic configuration but, usually, they do not have the same energy.

It followed from the atomic configuration-energy restriction that a reorganization of the entire atomic configuration is necessary to form a collision complex satisfying this restriction. To compute the free energy of reorganization, and hence the probability of formation of the reorganized state, expressions were first deduced for the properties of such nonequilibrium systems. The usual electrostatic formulas could not be used, and equations appropriate for these "disorganized" states of dielectric medium were derived.[20] An infinite number of atomic configurations can satisfy the restriction. The most probable set of configurations was obtained by minimizing the free energy of reorganization, subject to the restriction of constant energy. This information permitted the determination of the properties of the most probable state of the critical collision complex, including its free energy of formation from the reactants.

The expression obtained for the rate constant k of the electron transfer step is given by the following set of equations:[19]

$$k = p\,Ze^{-\Delta F^*/RT} \tag{3}$$

where Z is the collision frequency of two uncharged molecules in solution and p is the probability of occurrence of an electron transfer during the lifetime of the activated complex (10^{-13} sec.). The quantity p was assumed to be of the order of unity in preliminary applications and some evidence in favor of this was cited. ΔF^* is given by:

$$\Delta F^* = m^2\lambda + e_1^* e_2^*/D_s r \tag{4}$$

where

$$2m + 1 = -[\Delta F^\circ + (e_1 e_2 - e_1^* e_2^*)/D_s r]/\lambda \tag{5}$$

and

$$\lambda = \left(\frac{1}{2a_1} + \frac{1}{2a_2} - \frac{1}{r}\right)(\Delta e)^2 \left(\frac{1}{D_{op}} - \frac{1}{D_s}\right) \tag{6}$$

In these equations, e_1^* and e_2^* are the charges of the reactants, e_1 and e_2 are those of the products. As a result of reaction, the change in charge of reactant 1, Δe, is $(e_1 - e_1^*) = (e_2^* - e_2)$. The effective radii of the reactants, a_1 and a_2, were discussed. For complex ions and small hydrated metal cations they are the radii of spheres enclosing the first co-ordination shell. The standard free energy change of the electron transfer step in the reaction is ΔF°. The factor r, the distance between the centers of the reactants in the collision complex, was discussed and set equal to its minimum value $(a_1 + a_2)$. D_{op} is the square of the refractive index of the solvent, while D_s is the static dielectric constant.

Application[21] of these equations to isotopic exchange reactions was particularly instructive. The agreement between the experimental and theoretical results using no adjustable parameters was excellent for tightly knit covalently bound ions. For example, $\Delta F^*_{expt.}$ was[9] 12.7 kcal. mol^{-1} for the $Fe(CN)_6^{-4} - Fe(CN)_6^{-3}$ reaction, while the calculated value was 10.1 kcal. mol^{-1}. In the $MnO_4^{-2} - MnO_4^{-1}$ reaction $\Delta F^*_{expt.}$ was[22] 12.8 kcal. mol^{-1} and $\Delta F^*_{calc.}$ was 9.2 kcal. mol^{-1}. On the other hand, the agreement for small hydrated cations was reasonable, but not as good. For $Fe(H_2O)_6^{+2} - Fe(H_2O)_6^{+3}$, $\Delta F^*_{expt.}$ equals[10] 16.3 and $\Delta F^*_{calc.}$ is 9.8 kcal. mol^{-1}. For $Co(H_2O)_6^{+2} - Co(H_2O)_6^{+3}$, $\Delta F^*_{expt.}$ equals[11] 16.4 and $\Delta F^*_{calc.}$ is 9.9 kcal. mol^{-1}.

In the derivation of these equations each ion was treated as a sphere, inside of which no changes in interatomic distances occurred during the reaction. This assumption appears to be a reasonable one when the central atom in the ion is covalently bound to its ligands in both valence states, and therefore is less valid for the aquo ions. More recently, this assumption was eliminated[23] and a more detailed calculation was made incorporating, in a basic way, these changes in interatomic distances in the formation of the activated complex. The approximate *a priori* value computed for $\Delta F^*_{calc.}$ for both the $Fe(H_2O)_6^{+2} - Fe(H_2O)_6^{+3}$ and $Co(H_2O)_6^{+2} - Co(H_2O)_6^{+3}$ reactions was 18 kcal. mol^{-1}.

Experiments measuring the difference between the rate constants of an isotopic exchange reaction in water and in heavy water have been of particular interest. It was found experimentally[24] that the rate constants of the exchange reactions $Fe(H_2O)_6^{+2} - Fe(H_2O)_6^{+3}$ and $Fe(H_2O)_6^{+2} - Fe(H_2O)_5OH^{+2}$ were about twice as fast in water as in heavy water. An appreciably higher rate constant in water was also observed[25] for the $NpO_2^+ - NpO_2^{+2}$ reaction. Since the two solvents have similar values of both D_s and D_{op}, a reason for this behavior must be sought elsewhere.

Two explanations can immediately be offered; one of these[21] is an application of the refinement of the theory discussed previously. Some change must occur in the interatomic O-H distances in these processes. (The NpO_2^+ and NpO_2^{+2} ions are also partially hydrated.) It can be shown that such changes occur more easily for O-H bonds than they do for O-D

bonds because of the former's larger zero-point vibrational energy. However, a hydrogen (deuterium) atom transfer mechanism would also be consistent[24] with the data. These considerations were used[21] to propose tentatively a diagnostic test for distinguishing a small-overlap electron transfer mechanism from an atom transfer process where the atom transferred was not a hydrogen. Probable examples of such systems included halide ion-catalyzed isotopic exchange reactions between metal aquo ions.

Recently, a theory of overvoltage has been formulated[26] using the same basic assumptions as those employed in the redox theory, but taking into account the special conditions prevailing at electrode interfaces. The final equations deduced for the rate constant of the electron transfer step at the electrode bear a strong resemblance to EQUATIONS 3 to 6. The major differences are that Z becomes the number of collisions per second of an uncharged particle with unit area of the electrode; the Coulombic terms $e_1^* e_2^*/D_s r$ and $e_1 e_2/D_s r$ are replaced by appropriate terms for the work required to transport the central ion in its initial and in its final states to the electrode-solution interface; ΔF° is replaced by the "activation" overvoltage (the part of the overvoltage due to the slowness of the electron transfer step), λ has one-half its value in EQUATION 6, and a_1 equals a_2. Any changes in interatomic distances within the central ion during the entire process can be incorporated into the theory in a way similar to that employed[23] for homogeneous redox reactions.

When there is no concentration polarization this expression immediately gives the absolute value of the current density as a function of overvoltage. Application[26] to some redox systems, including the conversion of ferrous to ferric ion and of ferrocyanide to ferricyanide ion, gave satisfactory quantitative agreement with recent data.

There is a very strong parallelism between the theoretical equations noted earlier for electrode processes and those for homogeneous redox reactions, when the former occurs at zero overvoltage and the latter is an isotopic exchange having zero ΔF° (and a_1 equal to a_2). This suggests that it will be interesting to explore more quantitatively the relationship between the rates of various isotopic exchange reactions and of electrode processes involving corresponding ions. Some data available for such a comparison have been referred to earlier, and preliminary results in this direction are encouraging. A detailed and extensive comparison would be particularly desirable. Should this parallelism, modified by the small difference in theoretical equations, be established extensively, then this would be suggestive evidence for a "small-overlap"[19] electron transfer mechanism for both processes.

Evidence has been presented to show that the electrochemical reduction[27,1] and oxidation[28] of some organic compounds occur via an electron transfer with the electrode, rather than as the result of reaction with

nascent hydrogen or oxygen, which might be present at the electrode surface. Nevertheless, it seems likely that with certain possible exceptions the *homogeneous* oxidation-reduction of most organic compounds will possess an atom transfer mechanism.[29,30] Tracer studies have definitely established a mechanism of this nature in a number of cases.[17] Some possible exceptions are those organic redox reactions in which each of two reactants forms a more-or-less reversible electrochemical system. This has been assumed[31] on occasion. Partly for this reason, the recent detailed kinetic studies[7,32,33] of the homogeneous oxidation of a series of hydroquinone-like compounds by various oxidizing agents such as ferric ion or molecular oxygen have been of particular interest. In both cases, the data were consistent with two postulated reaction sequences. The redox step in one was an electron transfer; that in the other, an atom transfer. Application of EQUATIONS 3 to 6 to these systems is rather approximate since the charge distribution on the organic compound is far from spherical (in the electron transfer mechanism the active reagent is the negatively charged hydroquinone ion). The extension of the theory to such molecules has been discussed elsewhere.[34] The agreement between the experimental and calculated results is reasonable, but additional refinements are in progress. In these reactions, too, it would seem desirable to study in a detailed, comparative way the rates of homogeneous and electrochemical redox processes.

Crystallographic studies have also contributed to the understanding of redox reactions. For example, utilizing Libby's application of the Franck-Condon principle to electron transfer reactions, Brown[35] has pointed out that the slowness of the $Co(NH_3)_6^{+2} - Co(NH_3)_6^{+3}$ exchange reaction may be due to the large difference in Co-N bond lengths in the two reactants. A theoretical computation of the contribution of this effect on the reaction rate involves a knowledge not only of the interatomic bond distances, but also of the force constants of these bonds. Neither of these properties is known for most of the reagents whose isotopic exchange reactions have been investigated. Crystallographic and spectroscopic studies of these systems promise to be of definite interest.

A major question in electron transfer reactions is the ease with which an electron can jump from one reactant to the other when there exists a suitable atomic configuration satisfying the constant energy restriction. Some calculations[21] based upon earlier estimates[36] have suggested that this process could occur with relative ease, that is, that p in EQUATION 3, for example, was of the order of 1 to 0.01. However, a more direct estimate would be desirable. The electron transferred from an occupied electronic orbital of one reactant to a vacant electronic orbital of the other. The rate at which this process occurs in an appropriate atomic configuration depends upon the extent of overlap of the two orbitals. Some measure of this can perhaps be inferred from the interaction of two

occupied orbitals in adjacent hydrated ions in a crystal lattice. A quantitative measure of this interaction is derived from the interaction of the electron spins in the two ions, which in turn determines certain magnetic properties. Thus, an adequate quantitative theory for the latter phenomena may effectively contribute to the solution of the electron transfer problem.

One other example of electron transfer processes may be singled out for special mention. The visible and ultraviolet absorption spectra of halide ions in aqueous solution differ quite markedly from those in crystals. The absorption process was interpreted[37] in terms of an electron transfer from the ion to the adjacent solvent. Applying the Franck-Condon principle and detailed electrostatic considerations to the problem, Platzman and Franck[37] obtained excellent agreement between experimental and calculated positions of the absorption bands. This theory is also indirectly pertinent to the theory of the transfer of an electron from a univalent anion to an oxidizing agent,[34] since both quantitative formulations have certain assumptions in common.

In conclusion, it can be said that an understanding of electron transfer processes certainly will not be gained by the application of a single technique. Instead, the use of kinetic, electrochemical, crystallographic, magnetic, and spectroscopic methods will each contribute to the solution of the problem. This general field, therefore, promises to be a fruitful one for increased co-operation between physical chemists, organic chemists, and physicists.

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SECTION OF BIOLOGY

CRITERIA OF MALIGNANCY

I. MORPHOLOGY OF DETROIT STRAINS OF HUMAN CELLS IN TISSUE CULTURE*

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Human cells continuously maintained in tissue culture by microbiological methods exhibit features usually associated with malignancy. These features occur in cells derived from both noncancerous and cancerous sources. Thirteen strains of human cells (Detroit) developed from bone marrow, carcinomatous ascitic fluids, lymphomatous pleural fluid, nonleukemic peripheral blood, and a hamartoma of liver grow as networks of spindle-shaped, fibroblastlike (Fb-L), or intimately attached polygonal, epitheliallike (Ep-L) cells. Fb-L cultures may evolve to the Ep-L form.

During the development of the Detroit strains four phases were usually observed: (1) unchanged cells of the original explants; (2) large round cells; (3) Fb-L cells; and (4) Ep-L cells.

In air-dried smears of suspensions of trypsin-treated cells from various Ep-L strains stained with May-Grünwald-Giemsa (MGG) the isolated cells have round or oval nuclei with sharply defined edges. On the other hand, cells from Fb-L cultures have hyaline ectoplasmic borders. The tinctorial properties of these two types of cells are different. The Ep-L cells have a much deeper basophilic cytoplasm.

The nuclear chromatin patterns in all Ep-L cell lines are similar. Multiple nucleoli are present in all lines. In the Detroit-30A strain from carcinomatous ascites of a patient with carcinoma of the breast, there is a marked predominance of cells with single large nucleoli (90 per cent). In this respect these particular cells are very similar to HeLa cells.

The similarity of the various Detroit Ep-L strains is due to their characteristic formation of monocellular layers of polygonal cells resembling pavement epithelium. The Detroit Fb-L strains have an entirely different appearance. They form palisades and networks of spindle-shaped cells.

The colonial behavior of cultures of compact masses of Ep-L cells explanted in plasma clots is different from that of Fb-L cells. The former grow out as blunt-edged colonies in the manner of epithelium, and the latter form colonies of radially arranged spindle-shaped cells in the manner of fibrous connective tissue. When flask cultures of Fb-L cells transform to Ep-L cultures, the colonial behavior changes also.

*This paper, illustrated with lantern slides, was the first of two papers presented at a meeting of the Section on February 11, 1957. A more detailed presentation of the material contained in this abstract is to appear elsewhere.

Three-dimensional masses of tissue were obtained by growing cell suspensions in cellulose sponges. Ep-L strains grew readily. After 9 to 10 days masses large enough to be sectioned conveniently were formed. Fb-L cells usually formed only microscopic masses even after 40 days of culture. The different strains of Ep-L type formed tissue resembling undifferentiated epithelium, regardless of the original source of the cells. HeLa cells grew in the same fashion. There was no evidence of formation of cylinders, tubules, or adenomatous structures in any of the cultures, including those derived from cancerous ascites in patients with adenocarcinoma.

A few transplantation experiments in chicken embryos were performed to study the feasibility of this approach for investigating morphogenesis. In the chorioallantoic membranes a strain derived from bone marrow of a cancer-free individual formed lesions containing small irregular foci and cylinders of cells. Cells derived from a patient with cancer produced lesions containing well-formed cylinders of cells arranged on basement membranes.

Within each Ep-L cell line there are numerous aberrations of morphology, but the strains are alike in displaying prominently the types of abnormalities commonly associated with cancer. We found no evidence that these phenomena are more prominent in Detroit Ep-L lines derived from cancerous sources as compared with cancer-free sources. In fact, the strain exhibiting the greatest pleomorphism was derived from nonleukemic peripheral blood.

Chromosome counts indicated extensive heteroploidy. Among 240 cells studied in 5 Ep-L cell lines there was none with the normal diploid number of human somatic cells. In lines developed from bone marrow the modal values were between 68 and 70. In a strain from lymphomatous pleural fluid the modal value was 80 to 85.

The transformation of Fb-L cell cultures to the Ep-L state began as isolated foci of polygonal cells amidst an otherwise typical Fb-L culture. In scattered areas the cytoplasm of Fb-L cells became more deeply basophilic as indicated by the increased intensity of the blue color in MGG-stained preparations. While this process took place the affected cells became broader and shorter and their nuclei became rounder and larger; usually, also, the nucleoli became more distinct. There were numerous examples of altered cells with deeply basophilic cytoplasm still attached to adjacent spindle-shaped and otherwise typical Fb-L cells. As the focus of change enlarged more and more, cells in the region were similarly affected; those near the center of the focus formed closely approximated polygonal cells existing in small cords and sheets. After transfer the new cultures started out with increased numbers of polygonal cell foci and, as more transfers were made, the cultures started out as polygonal cells whose morphology has not reverted to the Fb-L state

after 26 months. On the basis of the change in tinctorial properties with MGG staining, we suggest that one of the changes taking place in the transition from the Fb-L to Ep-L condition involves an increasing concentration of ribonucleoprotein in the cytoplasm.

DISCUSSION

Because of the appearance of phenomena usually associated with cancer even in cells originating from normal or noncancerous sources, much attention is being directed to the possibility that human cells maintained in tissue cultures have become malignant. Although heteroploidy and great cellular pleomorphism are prominent in Detroit Ep-L lines, these morphological phenomena are known to occur in nonmalignant and reversible pathological conditions in the human. On the other hand, some observations by others on ascites tumors (T. Hauschka *et al.*) seem to indicate that increasing degrees of heteroploidy go hand in hand with increasing degrees of transplantability. If we are correct in considering transplantability, especially to unconditioned heterologous hosts, as an indicator of malignancy, the association of heteroploidy and transplantability may be very important. It seems likely that so-called stable strains of human cells maintained for long periods undergo continuous changes. The use of human cell lines for propagation of viruses may create difficulties on account of the possibility that both virus and substrate may be undergoing changes, but that difficulty may be considered an advantage in the study of neoplasia. In tissue cultures maintained for long periods, periodic reappraisals of morphological and biochemical changes can be correlated with titrations of malignancy by means of serial determinations of transplantability in suitable animal hosts.

II. BIOLOGICAL CONSIDERATION OF NORMAL AND ABNORMAL CELL LINES*

By Alice E. Moore**

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With the advent of tissue culture methods and the increasing applicability of these techniques, it has been almost imperative to find a normal cell line that can be used for control purposes. One can make all kinds of studies on the cancer cell, but the results obtained have a limited value unless they can be compared with those of a normal cell growing at the same rate and under the same conditions that can be studied at the same time. Such cells derived from normal sources are available, but now the question must be asked – are these cells still normal? One must emphasize the fact that these permanent cell lines grown in tissue culture are already different from their fellow cells in that they are maintained while the others die out. This is true for human sources, as noted by Chang,[1] who states that he has made over 30 attempts to get epithelial cultures started and has been successful only 5 times, and then only between January and May, 1954. This result also serves to emphasize the "magic" associated with these procedures. In our laboratories numerous attempts to obtain permanent epithelial strains in culture have failed, and other laboratories have faced the same problem. The difficulty of the procedure is emphasized by the fact that so few cultures have been obtained despite the availability of numerous cell lines from normal sources.[1-9] The same may be said for cells derived from animal sources.[10] It is possible that Puck's[11] clonal methods of isolation of single cells will bring forth many more isolations and eventually explain why some cells fail to establish themselves permanently in culture.

In the meantime it is necessary critically to examine these cells in every way possible to determine their exact status with reference to morphology, metabolism, nutrition, transplantability, and biological properties. This implies considerable work, the necessity for which one might question. It becomes imperative, however, if these cell lines are to be considered normal and used as a yardstick for comparison with the activities of other cell lines.

It is fortunate that at a recent conference these problems were dis-

*This paper, illustrated with lantern slides, was the second of two papers presented at a meeting of the Section on February 11, 1957. The investigation it describes was supported in part by a research grant (C-1355) from the National Cancer Institute, United States Public Health Service, Bethesda, Md.

**The author thanks the participants of the conference on *Cellular Biology, Nucleic Acids, and Viruses* (held under the auspices of The New York Academy of Sciences, January 7-9, 1957) for giving her their manuscripts and their permission to quote from them.

cussed from all angles; this article will incorporate ideas and results presented there. Agreement appeared to prevail that to define a cell line derived from a normal source as either normal or malignant is to invite controversy on one or another ground.

Morphology

Cytology. Morphological alterations in tissue culture do occur, and it is this change that usually brings the culture to the attention of the investigator. Changes in rodent fibroblasts have been observed and thoroughly studied for many years by Gey[12] and by Earle and his coworkers.[13] It is difficult to describe the changes that occur, but often they are of a nature that one associates with the cytological appearance of known malignant cell lines. For example, there may be marked variation in the size and shape of the cells; their arrangement may suggest a new individuality; and there may be multinucleated and giant cells. The nuclei may also be of various sizes and shapes, and they may differ in the proportion of nucleus to the cytoplasm. Nucleoli may vary in number, size, and shape, indicating an abnormal chromosomal arrangement. Atypical and bizarre mitoses are frequent, and the cytoplasm may be unevenly stained. Only some of these changes may be present, but it should be emphasized that they did not exist previously.

As an illustration of some of the morphological changes that occur, the appearance of the 57th transfer of the Chang conjunctival cells may be compared with the 13th transfer kindly supplied by Chang (FIGURE 1). It is apparent that, although the cells still grow in a sheet, their edges are not closely approximated. There is great variety in the size and shape of the nuclei, and the cytoplasm stains irregularly.

Morphological changes in human normal cell lines have been noted by: (1) Leighton,[2] working with a strain of fibroblasts isolated from foreskin; (2) Moore,[14] studying Chang cells; (3) Jordan,[4] working with nasal epithelium; (4) Swim and Parker,[5] working with foreskin and uterine muscle; (5) Berman,[3] working with sternal marrow; (6) Ginsberg,[8] working with isolations from tonsilar and adenoidal tissues; (7) Henle,[6] working with human intestine; and (8) Leslie, Fulton, and Sinclair,[9] working with a strain of cells derived from a human embryo (HLM). It might be worth calling attention to the fact that altered cell lines tend to resemble each other, as mentioned by Parker,[15] Chang,[16] and Berman.[3]

There are also reports of normal human cells that have retained their normal appearance after many passages in tissue culture. Syverton[7] cites a fibrocyte culture that has had 20 passages in tissue culture and that still maintains both its morphology and its proper chromosome number. He also states that many of his other cell lines, although showing an increase in chromosome number, have retained their normal appearance. In our laboratory it has been possible to maintain human

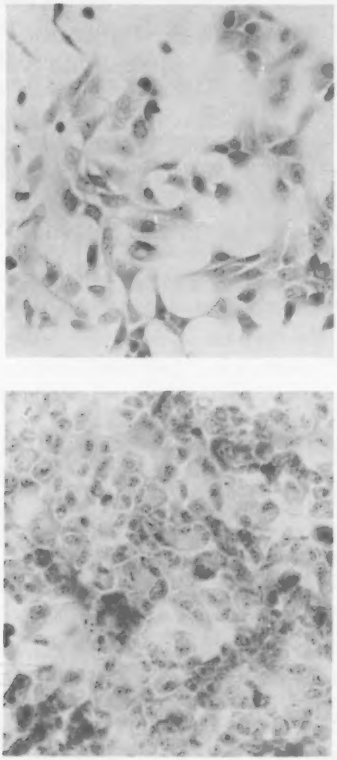
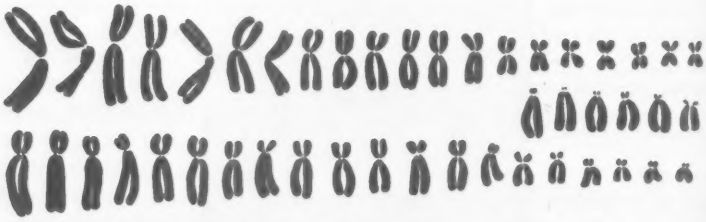


FIGURE 1. Morphological appearance of the 13th transfer of Chang's conjunctival line for comparison with the 57th transfer.

adult fibroblasts for 16 trypsinizations over a period of 4 months. There has been a slight change in their chromosome number to 48, but the metabolic activity of these fibroblasts, as measured by their anaerobic glycolysis, has remained constant. This strain has been used as a normal control throughout recently reported studies.[14] Others working with animal cells have reported stable lines for rabbit fibroblasts [10] and rabbit kidney epithelium,[15] and there are numerous reports of rodent fibroblasts in continuous culture that have maintained their morphology.[12]

Chromosome number. Cell lines may also be examined for their chromosomal constitution. The chromosomes of cancer cells vary from the normal in two different ways: (1) they are not fixed at a certain number, but vary around the modal number, that is, the stem-line number; and (2) as the cancer progresses the stem line shifts and is therefore usually

other than the chromosome number normal for the species. Both of these characteristics were noted in the conjunctiva and liver used by Chang when these cells were studied by Levan.[17] Levan's idiogram (FIGURE 2) of a normal embryonic fibroblast (above) and a Chang liver cell (below) shows graphically that the Chang cells have many more chromosomes than is normal. The chromosome number varied from 72 to 80 for both the liver and the conjunctiva. The only other cell lines from normal sources that have been studied for chromosomal constitution have been those of J. T. Syverton, who has noted hypertriploidy of the esophageal epithelium and the liver cell line of his isolates, as well as the Chang conjunctival cell line. His fibroblastic cell from the palate has maintained the number 46. It would seem worth while to study more of the cell lines from the chromosomal viewpoint.



Human chromosomes from a primary tissue culture of embryonic lung fibroblasts (Tjio and Levan, 1956). Chromosome number constant, 46.

Human chromosomes from a Chang cell strain of liver (Levan, 1956). Chromosome number varying, 72 to 80.

FIGURE 2.

Metabolic Studies

Growth rate. It has been the common finding among tissue culture workers that an altered cell line grows much more rapidly than its normal fellow as shown by the presence of more dividing cells, greater feeding ability as demonstrated by phase microscopy, and the frequency with which it can be transferred (Gey).[12] Many investigators[2,5,8] have noticed that their cultures remain dormant and are in danger of being lost or overgrown with fibroblasts when there is a sudden new burst of growth and the culture is re-established. This is usually accompanied by the predominance of a new cell type.

Warburg studies. Numerous studies have been made to compare the metabolic activities of normal and malignant cell lines, and recently some studies have been completed on altered cell lines. Hellerman and his group have collaborated with Gey[12] in a study of the normal rat fibroblastic strain (14p) and the tumor cell line spontaneously derived from it (T-333). Hellerman and Gey discovered that the tumor strain was much more active metabolically as measured by anaerobic lactate production. They also found that both the T-333 strain of cells and solid tumors produced from them had a much higher rate of anaerobic glycolysis when compared to the 14p strain of fibroblast. Metabolically the altered cell line behaved as a cancer cell line.

Vernon Riley of the Sloan-Kettering Institute, New York, N.Y., was kind enough to determine the anaerobic glycolysis of the cell lines by the Warburg technique. TABLE 1 (experiment 1) illustrates the results that were obtained from Chang's liver cell line, the HEP No. 2 cancer cell line, and human adult fibroblasts. It shows that the rate of anaerobic glycolysis of the liver cultures resembles that of the tumor cell line rather than that of the fibroblasts. In another experiment (No. 2) using the conjunctival cell line, the HEP No. 2 tumor, and human embryonic

TABLE 1

ANAEROBIC GLYCOLYSIS IN NORMAL, MALIGNANT, AND "TRANSFORMED" CELL LINES IN TISSUE CULTURE

		Normal (fibroblasts)	*Malignant (HEP No. 2)*	*Transformed (Chang's lines)*
μl. CO_2/hr./cell		5×10^{-6}	18×10^{-6}	13×10^{-6}
$Q^{N_2}_{CO_2}{}_R$ *	Exp. 1	16	54	40
	Exp. 2	9	37	69

*Five per cent CO_2 — 95 per cent N_2, tissue culture media with serum, values corrected for CO_2 retention.

fibroblasts, a still greater anaerobic activity was noted for the conjunctival cells.

In a metabolic study of an altered cell line derived from normal human embryos, Leslie, Fulton, and Sinclair[9] ascertained that the glucose consumptions of their 3 morphologically normal cell lines recently isolated from embryonic skin, kidney, and lung were very similar, whereas their morphologically different cell line (HLM), also derived from human embryo and in continuous culture, resembled that of the three human carcinomas studied. Syverton has also studied cells from normal and carcinomatous sources growing in tissue culture. Unfortunately at the time this paper was written his graphs were not available, so his complete paper should be consulted for his conclusions.[7]

Metabolic studies along these lines are just beginning, and we entertain high hopes that they will be of considerable help in following the change from the normal to the malignant. Since relatively large amounts of material are necessary for accurate measurements, it must be kept in mind that by the time cells have acquired that degree of autonomy they may already have changed their intrinsic nature.

Nutrition. Cells in continuous culture, whether from normal or cancerous sources, are known to change their nutritional habits. For instance, Chang noted that during the isolation of conjunctival, liver, kidney, and appendical cell lines from normal individuals their sensitivity to human sera was quite different.[16] Later this sensitivity disappeared. Marcus, Cieciura, and Puck[11] studied these cell lines after their establishment in tissue culture (40 to 70 transfers) as clones and discovered that their nutritional requirements were identical to those of the S3 line of HeLa cells. In addition, their morphological appearance, generation time, mitotic frequency, plating efficiency, incidence of multinuclearity, and giant cell formation were also similar to the malignant cell line, S3. Parker[15] has noted that monkey kidney cultures kept in a chemically defined medium without a protein supplement have failed to show altered cells in 3 months and that the cells remained in good condition.

There is no doubt that cell nutrition is one of the most important factors in tissue culture. It may act as the selector that allows only those cells with unlimited growth potentials to grow, or it may be the environmental factor that allows some of them to continue growing and discourages others. This phase of nutritional science has made great and wonderful strides in recent years[18, 19] but, as yet, it has not advanced sufficiently far to enable us to distinguish normal from malignant cells on a nutritional basis, although we recognize that both may have distinctive nutritional requirements.

Changes in Reactivity

Possibly a cell line, as it changes morphologically, may also change its reaction to viruses or chemicals. A loss in cytopathogenicity of

poliovirus for altered cell lines has been reported by Swim and Parker[5] in altered human uterine and foreskin cultures and by Parker[15] in a strain of altered monkey kidney cells. However, due to the great variety in cytopathogenic effects that one observes when a number of viruses are screened against a number of cell lines,[20] it seems unlikely that this method could be used to determine whether a given cell line is cancerous or not. Of course, if a cell line becomes resistant or susceptible to a certain virus or chemical, one could use this assumption as an indication that a change of some sort had taken place.

Transplantation

The ability of cultured cells to produce tumors in the homologous animal strain has long been a criterion for neoplasia. In the animal studies with rodent fibroblasts that we have cited, cell lines became capable of producing tumors that on histological examination were sarcomas and that could be transferred to other animals of the same strain indefinitely. It is impossible to study human altered cell lines in exactly this same way, but they can be tested for their ability to produce tumors by implantations into cortisone-treated and irradiated weanling rats[21] and also by implantations into volunteer cancer patients and normal volunteers.[22] Before presenting our experiments it is necessary to define what is meant by a positive or negative result, and I should like to quote from the recent paper by Moore.[14] "It seems there is no absolute criterion for calling a tumor a cancer, although the diagnosis is made every day. The pathologist makes up his mind on the basis of clinical findings, cell appearance, and a vast amount of experience. The sections of tumors arising from the inoculation of Chang cells were reviewed by four pathologists and were found to contain cells which looked like epithelial cells, which had certain characteristics that are associated with neoplasia, and which, if they had been submitted for diagnosis, would have been called cancer. It is immediately recognized that this is insufficient evidence for calling these particular cell lines cancerous because cancer is regarded as a progressive growth which leads to death of the host animal, and this is certainly not the case here. Keeping this in mind, a positive result is defined as the appearance at the site of tumor implantation of a nodule seven to fourteen days postinoculation with no sign of a nodule during the intervening time; and one which, when removed by biopsy, shows epithelial cells in an array and of a type suggesting neoplastic growth."

Very briefly, in the animal transplantation studies cited above, the Chang cell lines were inoculated (900,000 to 4,000,000 cells) subcutaneously into irradiated and cortisone-treated rats in 25 instances, and tumors that contained epithelial cells were produced in 13 rats. These tumors were considered positive. Known cancer cell lines al-

most invariably produced tumors, so there is no doubt that the Chang cells are much less vigorous in this regard. Control inoculations of cell suspensions of human testicle (4 attempts), placenta (2 attempts), and monkey kidney (1 attempt), failed to produce tumors, as did a variety of tissue minces from normal lung and breast. This finding was in contrast to the experiences of Coriell,[23] who obtained the same type and number of tumors from monkey and human kidney cell suspensions as he did from the Chang cell lines. Coriell pointed out that these all regress in contrast to HeLa, the only human cancer cell line studied. His findings differ from those of Ginsberg,[8] who studied lines of cells derived from normal tonsilar and adenoidal epithelium which, in quite a short period of cultivation (6 weeks), showed an alteration. When irradiated and cortisone-treated rats were inoculated, 85 to 100 per cent of them developed tumors that invaded muscle and submaxillary gland; by these criteria, the tumors were much more malignant than the HeLa strain that Coriell used as a control.

There are probably adequate explanations for the difference in results obtained. For example, as Ginsberg pointed out, his strain of HeLa might not have been as invasive as that used by Coriell. It may be that the normal cell suspensions with which we failed to produce tumors were of poor quality or were used in insufficient numbers. We agree with Coriell that known malignant cell lines are certainly more efficient in producing tumors in treated animals than are the Chang cell lines.

We have also used human volunteers* both with and without cancer in implantation experiments by inoculating 1 to 5 million cells subcutaneously into the flexor surface of the forearm.[24] Tatoo marks were placed directly over the implantation site, and biopsies were done whenever nodules became palpable. Two types of controls were used for these experiments; (1) human embryonic and adult fibroblasts that had shown no morphological change since they were isolated although, as mentioned before, the adult fibroblasts had 48 chromosomes; and (2) the known cancer cell lines. Thirteen implantations of Chang's cells were made in the cancer patients (TABLE 2). Seven of these implantations. on being biopsied, were found to contain epithelial cells and were considered positive according to our definition. Three had no palpable nodules and therefore were considered clear-cut negatives, and 3 had nodules that regressed. Nineteen cancer patients were inoculated with cancerous cell lines. On 15 of these, biopsies were done, 14 of which were found to contain cancer cells; in 2 nothing could be palpated, and therefore no biopsy was done on them and, in 2 instances, the nodules were allowed to regress. Whenever possible, the biopsy sites were rebiopsied at post mortem and, in 1 of 3 instances with the Chang cells and 2 of the 3 with the human cancer cell lines, tumor cells were found. The

*All of the human implantation studies were done in collaboration with Chester Southam.

TABLE 2

RESULTS OF INOCULATIONS OF CELL LINES INTO VOLUNTEER CANCER PATIENTS

	Chang cell lines	*Cancer cell lines*
Number of implants	13	19
Positive biopsies*	7/7	14/15
Nothing to biopsy	3/3	2/2
Nodules which regressed	3	2
Positive rebiopsies	1/3	2/3

*Usually done 10 to 14 days after implantation.

Chang cells are grouped in columns and cords embedded in connective tissue (FIGURE 3). A higher power (FIGURE 4) shows that the cells are epithelial in type with very little sign of degeneration. No tumors

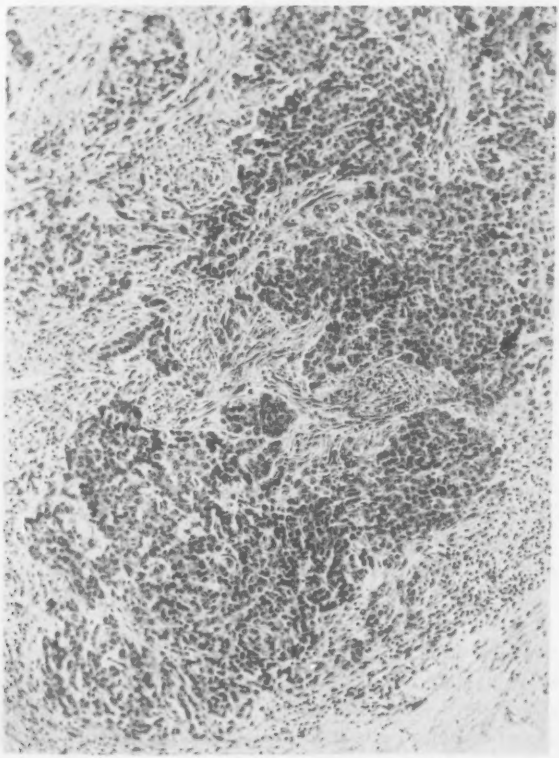


FIGURE 3. Histological appearance of the Chang conjunctiva cell line implanted into a human volunteer with cancer, 53 days after the first biopsy and 63 days after implantation. × 72.

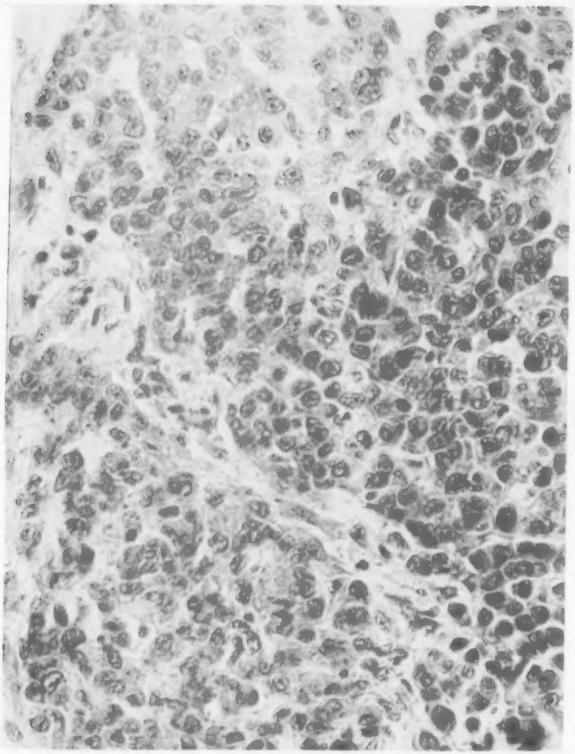


FIGURE 4. Same section as shown in FIGURE 3. × 240.

were formed from the three human fibroblast implants. It should be pointed out that there is a great deal of individual variation in the cancer volunteers' resistance to inoculation of either the Chang cell lines or known cancer lines. For instance, both positive rebiopsies of one of the tumor cell lines occurred in one patient whose susceptibility to cultured cells is attested by the fact that all implants took and that, at autopsy, a metastatic node was found from a chorioallantoic-membrane-grown HEP No. 3.

In the normal human volunteers receiving known cancer cell lines, four of ten implantation sites were found to contain cancer cells on biopsy fourteen days later. No tumors formed when either Chang cells (three implants) or HeLa cells (two implants) or human fibroblasts (three implants) were inoculated.

Discussion

The methods by which normal cell lines growing in tissue culture can

be studied to determine their biological character have been outlined. The main question is still apparent: "Can we say that these cell lines are malignant, or can we say they are normal?" My own feeling is that cell lines cannot be called normal unless, when studied by the above methods, they behave more like normal cells than cancer cells. Of the human cell lines described, only Syverton's palatine fibroblasts fulfill the criteria completely, since our fibroblastic line contains 48 chromosomes. One wonders if human fibroblasts alter less easily than epithelial cell lines, since it is mostly the latter that have developed abnormal characteristics. The cell lines of both Leighton[2] and Parker[5] began as fibroblasts, and Berman[3] has emphasized the fact that fibroblastic types often change to epithelial-like types.

If most of these cell lines cannot be called normal, can they be called malignant? No direct answer can be made to this question, for the simple reason that, although many resemble known cancer cell lines in their morphology, metabolism, and transplantability, they are in most instances less invasive than the known cancer cell lines and they have not metastasized. If it were permissible, as it is in conventional pathology, one could say that certain of these cells show a low degree of malignancy. Certainly, the known human cell lines differ in their ability to form tumors in man and, in most instances, regression takes place, yet we call these cancer because they arose from cancer patients.

A fact that must be mentioned in all of these studies is that our known cancer cell lines are rare in themselves. For instance, Toolan[21] who has had vast experience in heterologous transplants, points out that only a small number of human tumors will grow beyond the first generation. The same may be said for human tumors established in tissue culture; since this is also true for normal tissue growing under very artificial conditions, we should not be as surprised as we seem to be when it acquires new characteristics.

In conclusion, we can say only that we have no absolute criterion of malignancy as applied to cell lines from normal individuals that change during their cultivation in tissue culture. Now that we are aware of the possibility of such changes, we can do no more than examine each cell line with the idea of trying to find its place in this scale of normal to frank cancer.

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*DIVISION OF MYCOLOGY**

PRESENT KNOWLEDGE OF NYSTATIN, AN ANTIFUNGAL ANTIBIOTIC**

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An ever-increasing recognition of the prevalence and distressing effects of fungus infections has stimulated a vigorous search for antifungal antibiotics. During the past ten years a number of such agents has been discovered. Eight years ago a search for soil actinomycetes with antifungal properties culminated in the discovery of nystatin.[1] Such an actinomycete was found in a screening program employing a selective plating technique with *Candida albicans* and *Cryptococcus neoformans* as test fungi. This actinomycete, a member of the established genus *Streptomyces*, possesses certain cultural and biochemical properties unlike those of other described species.[2] It was therefore regarded as a new species and the specific name *Streptomyces noursei*† was proposed.

Isolation and Chemical and Physical Properties of Nystatin

This microorganism produced two antibiotics in broth culture under static conditions. One, readily soluble and present in the metabolism fluids, was identified as actidione.[3] The other, nystatin, was quite insoluble and appeared in good yield in the mycelium from which it was efficiently extracted with methanol. The crude product obtained on concentration of the extracts was purified by repeated solution in methanol and precipitation with saline or ethyl acetate. Chemically and biologically the purified product was different from other known antifungal antibiotics.

Knowledge of its physical and chemical properties is gradually contributing to the characterization of the nystatin molecule. Except at acid or alkaline reactions, the nystatin molecule is almost insoluble in water, but is somewhat soluble in the glycols and the lower aliphatic alcohols. Water increases the solvent action of alcohols. It is insoluble in chloroform, ether, ethyl acetate, and benzene. From methanol solution, nystatin may form needlelike crystals that do not have a sharp melting point. According to the empirical formula, $C_{46}H_{77}NO_{19}$, the molecule is a

*The Section of Mathematics and Engineering held a meeting on February 15, 1957, at which John N. Kenyon, Fatigue of Material Laboratory, Princeton, N. J., delivered a paper entitled "Fatigue Failure of Some Processed Metals Due to Recrystallization, with Certain Mathematical Implication." This paper will appear in a later edition of the *Transactions*.

**This paper was presented at a meeting of the Division on February 15, 1957.

† The specific name *S. noursei* was derived from the name of W. B. Nourse, owner of the dairy farm from which a soil specimen yielded the actinomycete.

relatively large one. It is unstable and has few characteristic reactive groups.

Dutcher and his associates[4,5] have published the following information on the chemistry of nystatin. In the ultraviolet absorption spectrum, three sharp peaks at 292, 305, and 320 mμ show that nystatin has a chromophore group containing four conjugated double bonds, and a slight maximum at 230 mμ indicates a diene system, as well. By catalytic hydrogenation, six mols of hydrogen are taken up by one of nystatin. The infrared absorption spectrum shows a broad intense hydroxyl band at 3.0 μ, a carbonyl band at 5.87 μ, and a carboxylate band at 6.37 μ. Since hydrogenation indicates no reducible carbonyl group, the band at 5.87 μ is probably due to a lactone configuration. Nystatin has four C-methyl groups and forms a monomethyl ester. The nitrogen is present in a primary amino group.

An atypical Molisch reaction and the many oxygen atoms suggest a carbohydrate moiety. Recently Dutcher and his colleagues[6,7] reported the identification, among the acetolysis products, of an aminomethyldeoxypentose with the amino group attached to C_3. The same sugar was discovered in Amphotericin B, another polyene antifungal agent. Thus, evidence of a similarity in structure for this group of substances is gradually emerging.

Nystatin is a rather unstable compound. It is most stable as a dry powder. In this state nystatin has been stored under refrigeration for at least four and one-half years without appreciable loss of activity. Aqueous suspensions are less stable than alcoholic solutions. However, they have been stored at –25° C. for at least eight months without apparent deterioration. Nystatin forms unstable salts with alkali and alkaline earth metals and with acids.

Biologic Properties

In vitro activity. A study of the antimicrobial activity determined by growth inhibition revealed high specificity for fungi. Amounts of 1.5 to 13 μg./ml. were effective against 34 of 37 fungi representing pathogens and saprophytes. *C. neoformans* and the yeastlike forms of the fungi that produce systemic disease showed greater sensitivity than did the filamentous fungi. Nystatin also possesses strong fungicidal properties, as demonstrated by its effect on growth multiplication of *C. neoformans*, *C. albicans*, and *Saccharomyces cerevisiae*.

For the bioassay of nystatin in blood, feces, and urine, Pagano and Stander[8] developed a tube dilution test with *S. cerevisiae* as the test microorganism. Adequate controls were employed to compensate for its instability and for the effect of body fluids.

The mode of action was investigated by Lampen and his co-workers[9] who concluded that nystatin inhibited the growth of microorganisms with

sensitive sugar-utilizing systems, such as *C. albicans, S. cerevisiae,* and *Penicillium notatum.* Lampen and his associates thought the inhibition of the utilization of glucose did not result from an inhibitor of hexokinase, but might represent an effect on sugar transport or ATP regeneration. Stewart[10] reported further clues as to the mechanism of action *in vitro* in the antagonistic effect on the action of nystatin of CHO or CHOH groups in sugars, or the favorable effect of CH_2 chains in alcohols.

The development of resistance by *C. albicans* has interested several investigators, none of whom has reported naturally occurring resistant isolates. Both Drouhet[11] and Stewart[10] found all their isolates of *Candida* to be sensitive to small amounts of nystatin. Stout and Pagano,[12] investigating the possible development of resistant strains of fungi, found that one of five isolates of *C. albicans* developed resistant mutants. A threefold degree of resistance appeared in one step and could not be increased further. There was cross resistance to polyene antibiotics only. In human therapy, Stewart[10] as well as Huang and others,[13] noted that isolates of *C. albicans* obtained before and after administration of nystatin revealed no difference in sensitivity.

Laboratory applications. Nystatin has found important applications in the laboratory[14-20] for the control of mold contaminants in bacteriological media, in samples of feces, sputum, and other materials from human and animal sources, and in fluids for tissue culture techniques. Concentrations that are fungistatic are not toxic for a variety of cells: HeLa, human kidney, liver, conjunctival, epidermal, epithelial, monkey kidney, and L cells, and chick embryo fibroblasts. In the usual fungistatic concentrations nystatin apparently has no inhibitory effect on bacteria or viruses.

In vivo activity. The antibiotic was always injected into animals as a suspension. Early tests in white mice showed the LD_{50} by intraperitoneal route to be 20 to 26 mg./kg. of body weight, but subcutaneous doses of 150 mg./kg. failed to kill the animals. No detectable cumulative systemic toxic effects resulted from repeated subcutaneous doses totaling 1.25 gm./kg. during an eight-day period. At the site of injection there were induration and necrosis that healed spontaneously.

Significant blood levels of nystatin were demonstrated in mice and rabbits by the technique of Dornbush and Pelcak[21] with *C. neoformans* and *S. cerevisiae* as test microorganisms and an incubation period of 24 hr. In mice injected subcutaneously with 100 mg./kg. of body weight, the concentration of nystatin was 24.3 μg./ml. of serum 1/2 hr. after and 6 μg. 4 hr. after injection. In rabbits injected intramuscularly with 30 mg./kg., the concentration reached a maximum of 12.5 μg./ml. at 8 hr.

Therapeutic Activity

In animals. The potentiality of nystatin as a therapeutic agent was

demonstrated repeatedly in animals experimentally infected with pathogenic fungi. The results of some of the protection tests carried out in mice infected with *C. neoformans* and *Blastomyces dermatitidis* are summarized. The antibiotic was always administered subcutaneously, twice daily the first week and thereafter at longer intervals.

In one experiment, 30 mice were injected intraperitoneally with 5,000,000 cells of *C. neoformans* (hemocytometer count), and divided into groups of 10: group I, untreated, served as controls; group II received nystatin (a total of 1.6 gm./kg. of body weight) over a period of eight weeks, treatment beginning promptly after infection; and group III was similarly treated, but with a total of 1.35 gm./kg., injections beginning one week after infection. All control mice were dead at the end of the ninth week, while all treated mice were alive; at the end of the 13th week, 60 per cent were still alive. The last mouse in groups II and III died the 56th and 21st weeks, respectively.

In a second experiment, 20 mice were given, intravenously, 1,250,000 cells of *C. neoformans;* 10 served as controls, and 10 received nystatin. Treatment began 6 days after infection and continued for three months if possible. The control mice were dead at the end of the fifth week when 90 per cent of the treated mice were living; by the end of the ninth week, 50 per cent of the latter were still alive and 20 per cent survived until the end of the 15th week.

In a third experiment, treatment with nystatin was begun on the day of intravenous infection with 1,250,000 cells of *C. neoformans*, and continued for 4 months. None of the control mice survived longer than 5 weeks, whereas at the end of 19 weeks, 8 of the 9 treated mice were alive. In India ink preparations of the brain of the one dead mouse, *C. neoformans* was not found, nor was the microorganism isolated. The 8 surviving mice died at intervals up to 80 weeks. Microscopic examination of India ink preparations of the brains of 5 of these 8 mice showed no microorganisms in 2, cells thought to be *C. neoformans* but not entirely typical in 2, and cells with wide capsules in only 1. No gross lesions were found on the livers or spleens of these animals, nor was the fungus isolated. In the control mice, cells with wide capsules were found in large numbers in the brains of all, and multiple lesions were noted on the livers and spleens of all and on the kidneys in 8.

The therapeutic value of this agent in experimental blastomycosis in mice was equally promising. Thirty mice were infected intraperitoneally with the yeastlike cells of *B. dermatitidis* mixed with 5 per cent mucin. Ten served as controls; 10 were treated promptly after infection; 10 were treated 2 days after, and treatment continued over a period of approximately 3 weeks. Ninety per cent of the animals receiving nystatin were still living at the end of 2 weeks, when all untreated mice were dead; some lived for as long as 5 weeks.

In addition to the above infections, one of the earliest experiments[1] demonstrated that nystatin was highly effective in mice against a massive intraperitoneal dose of *Histoplasma capsulatum*.

Campbell and her co-workers[22-24] have reported that nystatin prolonged the lives of mice infected with *C. albicans*, *Coccidioides immitis*, and *Sporotrichum schenckii*, but that it was least effective against *S. schenckii*. Gordon and his colleagues[25] discovered that nystatin markedly reduced the mortality of mice infected with *C. immitis*. Treated animals sacrificed at the end of the experiment had fewer pulmonary lesions, but had extensive visceral lesions. Sternberg and his associates[26] have found that nystatin prolonged the lives of mice infected with *C. albicans* and reduced the degree of kidney involvement.

Drouhet and Schwarz,[27] investigating experimental histoplasmosis in hamsters, have obtained evidence that early and adequate treatment with nystatin prolonged life. Spread of the fungus to the lungs was practically eliminated, and involvement of the liver and spleen reduced.

In our laboratory[28-30] the prophylactic and therapeutic value of this antibiotic in moniliasis induced in conjunction with the tetracyclines has been studied in mice and rabbits.

In mice, the rapidly fatal monilial infection following intraperitoneal injection of *C. albicans* in combination with these antibiotics was prevented in a high percentage of animals by a single subcutaneous injection of nystatin given before, or at time of, infection or, in the case of tetracycline, by incorporating the nystatin in the lethal mixture.

Rabbits that developed moniliasis of the mucous membrane and mucocutaneous tissue of the mouth, following ingestion of *C. albicans* during administration of tetracycline, responded within from 6 to 18 hr. to nystatin given in capsules or honey, while untreated rabbits did not recover for from 12 to 14 days. The animals receiving nystatin with tetracycline did not develop moniliasis.[30]

Several investigators have made studies of the normal intestinal microbial flora of animals and man as influenced by oral administration of the tetracycline antibiotics and nystatin. The feces of rabbits infected with *C. albicans* and treated with tetracycline[30] revealed a marked reduction in the normal bacterial flora and a heavy overgrowth of the fungus, while the feces of infected rabbits that received nystatin in addition to tetracycline had only a few fungus cells and a reduced bacterial flora. Sternberg and his co-workers[26] have found that the yeastlike fungi, but not the mycelial fungi normally present in the feces of healthy mice, disappeared temporarily during administration of nystatin.

In man. The investigation of nystatin has been concerned chiefly with moniliasis. However, the broad *in vitro* spectrum and the results in animals suggest that therapy in other fungus diseases might well prove satisfactory if the requisite mode of treatment were established. Newcomer and his colleagues[31] ascertained that, in the treatment of dis-

seminated coccidioidomycosis with nystatin, 3 cases were favorably influenced by intravenous administration, but that 2 cases with meningeal involvement were not influenced and terminated fatally. The nystatin did not pass from the blood into the spinal fluid. In man it is difficult to secure very significant blood levels. These investigators discovered levels from 0 to 3 μg./ml. of serum after a dose of 200,000 units given intramuscularly twice a day; and as high as 40 to 45 μg./ml. when 200,000 units were injected intravenously 4 times a day.

Graham and his associates[32] have reported the effect of nystatin in 93 patients with dermatophytoses caused by *Trichophyton rubrum, T. gypseum, T. tonsurans, Microsporum lanosum, M. fulvum, Epidermophyton floccosum,* and *Malassezia furfur.* In the majority of cases, despite some clinical improvement, the fungus was identified even after prolonged treatment. Flarer[33] had promising results with combined oral and topical therapy in trichophytosis and epidermophytosis.

Most favorable reports on the effectiveness of nystatin in various manifestations of moniliasis are now appearing. The increased incidence and severity of these infections, particularly as sequelae to therapy with broad spectrum antibiotics, have demonstrated need for such an agent. As a rule, good to excellent results are obtained with almost no side effects.

Drouhet[11] has noted remarkable efficacy of oral and topical applications of nystatin in 35 cases with generalized or localized infections due to *C. albicans,* with 3 relapses. From this pioneer work he made the following observations. In oral thrush the antibiotic should be given as a suspension. Relapses that occur when treatment is discontinued too soon respond satisfactorily to retreatment. The persons most prone to moniliasis were premature infants, debilitated persons, such as leukemic or diabetic patients and those receiving prolonged antibiotic therapy.

Dobias[34] has reported that of 48 infants and young children with cutaneous moniliasis, 24 were cured and 23 were improved by nystatin applied topically, orally, or by both routes. In 6 patients in whom pulmonary moniliasis was suspected (1 presenting X-ray evidence of pulmonary infiltration) all symptoms disappeared with treatment. Five patients relapsed, but responded to retreatment. Huang and her associates[13] also obtained favorable results in oral moniliasis of premature and older infants. In addition, González Ochoa and his colleagues[35] found that in 75 cases of oral moniliasis in children the lesions disappeared after an average of 2.4 days of oral therapy. The 4 cases that relapsed responded upon retreatment for 3 days.

Several reports[36-38] of the successful treatment of monilial vaginitis in pregnant and nonpregnant women have appeared. Pace and Schantz[39] successfully treated 58 of 59 such patients by intravaginal therapy. Fourteen relapsed cases responded to retreatment. Robinson[40] discovered nystatin effective in 62 patients with various forms of *C. albicans* in-

fections, with the most dramatic results in 20 cases of vulvovaginitis.

Robinson has also reported that *C. albicans* infections of the nails were cleared by nystatin, but that these infections required prolonged topical and oral treatment. Wright and his co-workers[32,41] used nystatin effectively in a series of 122 patients with oral, vaginal, and cutaneous moniliasis. *C. albicans* was isolated from 43 per cent of the persons, although the lesions had healed. Relapse was more common in patients with severe systemic illnesses of other etiology. Higdon[42] has reported success with topical application in intertriginous moniliasis.

Sternberg and other investigators[26] have demonstrated that nystatin removed or markedly reduced *C. albicans* in the feces of man, even with concurrent therapy with oxytetracycline or chlortetracycline. *C. albicans* reappeared with the discontinuance of the nystatin. These results have been confirmed by others.[43,44] Cohn and Longacre[45] have recommended a combination of neomycin and nystatin for preoperative sterilization of the colon where overgrowth of yeasts was a possibility.

The side effects elicited by nystatin depend upon the route of administration. Intravenous injections in cases of coccidioidomycosis[31] caused sclerosing of the veins, and initial injections were accompanied by severe shaking, chills, fever, and malaise. Intramuscular injections induced severe pain and tenderness at the site of injection. Administered topically or orally, however, it appears to be remarkably free of toxic reactions. No instances of allergic reactions or of contact dermatitis or urinary tract symptoms have been reported. The incidence of nausea, vomiting, and diarrhea has been low. Newcomer and his associatès[31] observed no side reactions other than transitory nausea and diarrhea when treatment was prolonged for 6 months and doses reached as high as 12 gm. daily.

The low toxicity and high effectiveness of nystatin for prevention and therapy of moniliasis led Welch[46] to conclude that it should logically be administered prophylactically when the broad spectrum antibiotics are required for debilitated patients, diabetics, infants (particularly premature infants), and pregnant women.

Summary

Nystatin is a polyene antibiotic produced by *Streptomyces noursei. In vitro* it specifically inhibits the growth of a wide variety of pathogenic and saprophytic fungi, exhibiting both fungistatic and fungicidal properties. It has marked therapeutic action in mice experimentally infected with *Cryptococcus neoformans, Blastomyces dermatitidis, Histoplasma capsulatum, Coccidioides immitis, Sporotrichum schenckii,* and *Candida albicans*. In oral moniliasis in rabbits its prophylactic and therapeutic effect is striking.

Nystatin is a valuable and specific therapeutic agent for the various

forms of moniliasis in man; as such, it is nontoxic and does not give rise to resistant strains of *C. albicans*.

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*SECTION OF ANTHROPOLOGY**

PSYCHOANALYSIS AS ANTHROPOLOGICAL FIELD WORK: DATA AND THEORETICAL IMPLICATIONS**

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In this paper I propose to examine the usefulness of research psychoanalysis as a specialized anthropological field technique. It seems unnecessary to describe in this context the technique of research psychoanalysis since, at least in principle, there exists only one generalized system of classical psychoanalytic technique, one directly deducible from the basic conceptual scheme of the science of psychoanalytic psychology. My study is limited to an examination of the type, quality, and anthropological import of data obtained by psychoanalyzing persons who belong to nonoccidental cultures and to a presentation of the theoretical consequences of these data.

As with every other specialized anthropological field technique, research psychoanalysis has areas of maximum and minimum productiveness. Thus, psychoanalysis cannot provide the necessary data for a well-rounded ethnography of a given tribe. Therefore, even though an analysand who belongs to some well-studied Indian tribe occasionally mentions a previously unreported culture trait, this fact deserves only passing mention in the present discussion.

By contrast, research psychoanalysis is an extremely efficient means of eliciting information concerning the matrix of values and meanings to which a given item is assigned. Such data are of great interest to the anthropologist, since no action, attitude, or material object is a cultural item unless it is embedded in a matrix of values and meanings. Thus, Lowie[1] has shown that neither the occurrence nor the nonoccurrence of cohabitation between the ape and his daughter can shed light on the anthropological problem of incest, since the fact that a certain female is his daughter *means* nothing to the ape. Hence, it cannot motivate the ape to refrain from incest, nor can it induce him to cohabit with his daughter either for cultural or for neurotic reasons†.

In brief, sexual interaction between biologically related individuals can be *incest* and the nonoccurrence of such sexual relations can represent an *avoidance of incest* only in a human – that is, cultural – setting.

*A paper entitled "Basic Biodynamics" was presented by Edward J. Kempf, Vice-President of The New York Academy of Sciences, at a meeting of the Section of Psychology on February 18, 1957. This article will be published as part of the *Annals of The New York Academy of Sciences*.

**This paper was presented at a meeting of the Section on February 25, 1957.

†An ape could not commit incest because – like Thyestes – he was advised to do so by an oracle,[2] or because – like a Ba Thonga big game hunter[3] – he wishes to become as terrible as the beast which he hunts, or because – like an Azande king[4] – it is his royal privilege, or because – as in Swedish peasant families[5] – a sick woman's adolescent daughter first becomes her father's housekeeper and then his mistress.

The same thing is true of all other inherently possible actions, attitudes, or ideas; they do not become cultural items unless they are embedded in a matrix of values, meanings, and other such factors, which establishes between the trait and the rest of the culture a horizontal-functional and vertical-hierarchical compendence.

Any item has at least four matrices. Thus, if a man gives his best girl a bouquet of flowers for her birthday, his action has a *biological* matrix, since it is related to courtship and sexual union; it has an *experiential* matrix, because it is motivated by the knowledge that she likes flowers; it has a *cultural* matrix, because the observance of birthdays is a custom; and it may also have a neurotic matrix, if he chose flowers instead of candy because, unconsciously, he wishes to be fed by his future wife instead of having to feed her.[6] Psychoanalysis is exceptionally suitable for obtaining information about the matrices to which the analysand assigns a given item, since his statements never appear "out of context," in the sense in which an anthropologist filling out a trait list questionnaire obtains data more or less out of context.

It is just beginning to be recognized that any cultural item has several cultural matrices. A dim awareness of this fact prompted Edward Sapir to affirm that every member of a society has his own culture. While this statement is certainly unacceptable, it has the merit of directing our attention to the multiplicity of matrices into which a given item may be embedded.

At present anthropologists have no effective schema for analyzing and classifying the various cultural matrices in which a given trait may be embedded. On the other hand, Linton[7] developed a scheme for the classification of *all* traits composing a culture. He differentiated between *universals,* such as language; *specialties,* as exemplified by the techniques of various crafts; *alternatives* between which each person belonging to that culture is free to choose without gain or loss of prestige; and – as an afterthought – *patterns of misconduct* that say in effect: "Don't do it but, if you do, you must proceed thus and so." Once we recognize that a given cultural item may belong to two or more of these categories and not only to one of them, Linton's scheme becomes applicable also to the analysis and classification of the various matrices in which a given item may be embedded.

A simple example will illustrate this point. In our society, the universal matrix of rolling pins is cookery. Its secondary matrix is a certain "pattern of misconduct," since the folklore of humor specifies that women may use rolling pins to chastise their erring husbands. It should be stressed, however, that such an act represents not simple misconduct but socially patterned misconduct because, even though the use of rolling pins in domestic strife is not approved behavior, it is nevertheless behavior that is recognized as "typical"; behavior toward which society reacts by means of a standardized attitude called humorous

tolerance. By contrast, the use of rolling pins in battles between women or for beating children or dogs is misconduct pure and simple; it is not recognized as typical and elicits unqualified condemnation.

It is important to stress that what is today the secondary matrix of a trait may formerly have been its primary matrix. The original primary matrix of playing cards – derived from the tarot – was not "entertainment" but "divination," whereas today fortunetelling is certainly a secondary matrix which, in the framework of law at least, is a pattern of misconduct, just as, in a psychiatric context, playing solitaire for oracular purposes is neurotic behavior.

One additional, and more or less heuristic, distinction to be made at this point is that between items and matrices belonging to the *mainstream* of culture and those which belong to *marginal segments* of culture. Thus, science and religion belong to the mainstream of our culture, while superstition belongs to a marginal and, in a sense, even "pattern of misconduct" segment of it.[8] It is a matter of some importance whether, in a given culture and at a given time, the *principal* matrix of an item belongs to the *mainstream* of culture or to some *marginal segment* of it. Thus, it seems probable that, even after two world wars, the primary matrix of the rifle in the United States is still a relatively marginal segment of culture (hunting), while, in an age of cold wars, its secondary matrix (warfare) is a major aspect of the mainstream of culture.

It is hardly necessary to emphasize that personal factors in the broadest sense of the term – including even the ethnic character – will determine into which context or matrix (cultural, neurotic, or other) the analysand decides to place a given item. We shall neglect for a moment all matrices other than the cultural ones, and shall examine only the manner in which such multiple matrices appear in psychoanalytic work and the anthropological significance of the data so obtained. However, before we can study in detail the variety of matrices to which a given item may be assigned, we must first discuss an extremely basic type of duality that may be observed in every known culture.

Although classical scholars have systematically stressed the rationality of the Greeks and their pursuit of the ideal of the golden mean, Dodds[9] was able to show that irrationality and orgiastic ecstasy played an equally decisive role in Greek cultural dynamics and in the formation of Greek character. We know today that the ostentatiously Apollonian façade of Pueblo culture[10] masks a witches' cauldron of meanness, envy, hate, and fear.[11] The social implementation of the Kwakiutl chief's notoriously paranoid grandiose competitiveness[10] is made possible only by the extreme co-operativeness of the Kwakiutl commoner.[12] Fortune[13] has been accused of wantonly distorting our traditional conception of Omaha culture,[14] whereas in reality he simply illuminated the reverse side of the medal. I have ventured to suggest that, far from being primarily

reality-oriented, efficiency in the United States chiefly seeks to keep unpleasant reality at arm's length.[15]

In reality, a great deal of evidence suggests that the extreme elaboration of some cultural item does not always necessarily prove that this item actually occupies a nuclear position in that culture.[16] Thus, even though most Mohave did engage in warfare, while only a few of them were transvestites, as many culture traits are associated with institutionalized homosexuality[17] as with warfare.[18,19] In fact, it is quite probable that at least some inherently secondary practices can survive only if they are socially implemented and culturally elaborated out of all proportion to their real importance.[16] The proper way of determining the nuclearity or marginality of a given cultural cluster is not to count the number of traits associated with it, but to determine how many items are *forcibly* brought within its scope. Thus, it is suggested that the most objective measure of the importance and pervasiveness of the idea of temptation and salvation in medieval society is not the number of cathedrals, but the fact that the *Gesta Romanorum*[20] interpreted chess as a symbol of the quest for salvation, by forcing this game into the procrustean bed of theology and by establishing an artificial compendence between the two.

On a more general level, each culture appears to contain important and culturally sanctioned systems of thought and institutions that actually negate the very basis of that culture and, sometimes, even all of reality. A great pope asserted that all worldly government was basically evil and quite incompatible with the City of God. Brahmanism, a nuclear feature of Hindu civilization, went so far as to deny that reality was anything more than Maya, or illusion. More generally, culture itself produces all the value systems in terms of which culture as a whole is criticized and sometimes arbitrarily condemned.

On a less abstract level, one and the same item may have two mutually contradictory matrices.

All students of the Mohave and of the River Yumans in general recorded the belief that twins are visitors from heaven, to be welcomed with open arms and showered with honors, gifts, and privileges.[21] However, the simple question: "What is better, a twin or an ordinary person?" enabled me to obtain a highly developed secondary set of beliefs, according to which twins are the unwelcome, graspingly acquisitive ghosts of dead persons, who become reincarnated solely because, when they die for the second time, they will be able to take with them a second set of funeral gifts to the land of the dead.*[22] The methodological import of the fact that anthropologists did not even suspect the existence of this second set of beliefs concerning twins will be discussed in a later section of this paper.

*This finding proves that the frenzied destruction of property at funerals represents "spiteful giving."[23]

An even simpler example is the dual matrix of the cultural item "dog." In terms of one cultural matrix the dog is man's best friend. The nature of the second matrix to which the dog is assigned is revealed by such expressions as "dirty dog" and the like.

The anthropologically sophisticated psychoanalyst often discovers that the analysand's subjective ambivalences are closely related to the characteristic basic ambivalences of his culture. A Plains Indian whose tribe hunted for many centuries had a dream that clearly expressed feelings of guilt over the killing of animals: the fox that he shot turned into a baby.[16] While partly subjective and neurotic, this guilt was, at the same time, deeply embedded in the culture of his tribe: the buffalo, the staple food of that tribe, was not simply "meat on the hoof," but also a sacred animal that played a great role in power-giving visions, rituals, and other tribal institutions. In fact, many tribes go to great lengths to conciliate and to honor the game killed by the hunter.[24]

In some instances the analysand, instead of assigning a given item to the *manifest* content of its primary matrix, tends to emphasize the latent or implicit meaning of that trait and of the matrix to which it is traditionally assigned.

All Plains Indian societies are characterized by an unusually high degree of sibling rivalry. Sioux Indians boast that their parents loved them so much that they refrained from marital relations for years in order to delay the birth of younger siblings.[16] The Blackfoot expect the man who was a "favorite" or "honored" child to be an especially generous giver.[25] Masculine competitiveness in general is also highly institutionalized.[26] This characteristically intense sibling rivalry is the cultural matrix of the pathologically callous reactions of a Plains Indian woman analysand to a rather gruesome tribal tale about a baby who left its cradle every night to cannibalize other babies, and then stealthily returned to its cradle with bits of human flesh stuck between its teeth. This woman told me that she never wearied of this tale and that she felt sorry for the little cannibal, who must have experienced a great deal of discomfort, due to the bits of human flesh caught between its teeth. "I wanted to pick his teeth and make him comfortable again."

It stands to reason that this pathological reaction was determined largely by this woman's own life history. Due to her mother's illness, she was weaned quite prematurely, at least by tribal standards, and, to make things worse, she watched her younger siblings being nursed for two years or more. Therefore she developed an intense reaction formation against her longing for the maternal breast. She boasted that she drank coffee at six months, declared that she hated milk and never drank it, but extolled the deliciously "bland" taste of a blood-red soft drink. In addition, she resented anyone who had access to a woman's breasts. In a moment of negative transference she accused me of staring at her breasts and, in describing ritual cohabitation between the tribal priest's

wife and several men, she condemned not the "sexual immorality" of the ritual, but the barebreastedness of the priest's wife.[27] In brief, because of her own neurosis, she responded not to the manifest but to the latent content of the story; the matrix in which she placed the narrative was not "folklore," but "sibling rivalry." However, she was able to disguise the real nature of her response, even from herself, and she professed to enjoy the story as folk literature. This made the sadistic fantasy seem vicarious and culturally sanctioned and, therefore, at least moderately ego-syntonic.

Needless to say, the reverse maneuver may also be observed, especially in the development of sublimations. Thus, the inventor of an ego-dystonic sadistic fantasy may turn that fantasy into a short story. Otherwise stated, he may depersonalize and culturalize it, and assign it to the cultural realm of literature rather than to the subjective realm of daydreams. In this manner the "author" ceases to feel acutely "responsible" for the ego-dystonic latent content, just as one feels less responsible for one's dreams than for one's waking thoughts.[28] It might be remarked in passing that the limited responsibility one feels for the content of one's dreams was systematically exploited in the treatment of a Plains Indian, who was encouraged to "dream out" his conflicts before coming to grips with them in the therapeutic hour.[16] Society itself readily sanctions such maneuvers, and agrees to see "inspiration" of extrapsychic origin where, as Kris rightly pointed out,[29] there is nothing more than "regression in the service of the ego."

The very fact that a subjective production is extrajected and assigned to the realm of culture seems to give it all the attributes of "mature" and "well-socialized" cultural behavior. Abraham's patient must have felt extremely mature and socially responsible when he transmuted his curiosity about the origin of babies into a scientific interest in the chemical state called "status nascendi."[30] Moreover, had the child who defined flatus as an adult prerogative[31] grown up to be a composer, he would have felt very mature when, instead of expelling flatus, he scored the fortissimo climax of his symphony for the brass ensemble.*

Both analysands and ordinary informants may, on occasion, voice not the manifest but the latent content of an item or matrix. Several cooperative Mohave informants explained the hikwi:r disease as follows: certain bodies of water are inhabited by supernatural aquatic snakes, whose chief has two heads – one at each end of his body. If these snakes attack a person either in real life or in dream, the victim contracts the hikwi:r illness. It is quite certain that this account embodies the official Mohave belief about the hikwi:r illness. Yet the reliable and extremely well-informed shaman Hivsu: Tupo:ma gave a wholly different

*Pseudosublimations such as shamanism will be ignored in this context, since their neurotic basis has been discussed elsewhere in some detail.[32]

explanation of this illness: should a woman, in the course of a swimming party, cohabit with a man under water, she will contract the hikwi:r illness.

Now, even though these two accounts of the hikwi:r illness diverge widely on the manifest level, Hivsu: Tupo:ma's "unorthodox" theory of that illness is neither a lie nor a strictly personal opinion. It is simply an explicit and nonsymbolic statement of the latent content of the official theory, made possible by the informant's uninhibited love of ribaldry. It translates the snake symbol into its real referent, the male organ, and equates underwater intercourse with an underwater attack. Hence Hivsu: Tupo:ma's account of the hikwi:r illness is as genuine a part of Mohave culture as are the officially sanctioned theories of the other informants. This finding supports the statement made elsewhere[33,34] that the latent content of even the most divergent versions of a given myth is always the same, just as the latent content of a tendentious lie is identical with the truth which the liar seeks to distort or to deny.

In fact, it is permissible to affirm that the discovery of the latent matrix of a given item is as legitimate an anthropological goal as is the discovery of the official and manifest matrix of that trait.

We cannot and do not wish to deny that an awareness of the multiplicity of manifest and latent matrices to which an item may be assigned appreciably complicates the task of the anthropologist who seeks to clarify the basic pattern of a given culture. However, as a great mathematician once pointed out, nature is completely unconcerned with analytic difficulties. Hence, like the analyst, the anthropologist would be well advised to remember the wise counsel of another great mathematician: "Seek simplicity, but distrust it." A failure to distrust simplicity has led to many grossly oversimplified formulations of cultural patterns, as well as of the character structure of ethnic groups and even of individuals.

It may be objected that the analysand's tendency to emphasize the secondary matrix of a trait instead of its primary matrix, or to specify the latent rather than the manifest content of the matrix to which a trait belongs, is subjectively determined. While this is certainly so, it does not mean that the information he gives is not quite as much a part of culture as is the official matrix of a given item, or the manifest content of a given belief. This thesis can be proved by showing that idiosyncratic and even neurotic motives may induce an analysand to place a given item in its primary matrix. A Plains Indian cowboy always referred to the cultural item "horse" in the proper and primary cultural context. Nevertheless, his repeated references to geldings and to "proud cut" horses were simply veiled attempts to inform me that he had a severe potency disturbance.[16]

A neurotic compulsion to emphasize the subsidiary rather than the primary matrix to which some item may be assigned can also yield valu-

able anthropological information. A halfbreed Indian, son of a primitive Indian man and of an educated but frustrated and disappointed white woman, refused to place his father in the most natural cultural matrix, as head of the family, and assigned him instead to the culturally less nuclear matrix: "inferior races." This halfbreed's intense race prejudice enabled him to deny the violence of his oedipal conflicts, and to define sexual relations between his father and his mother solely as the "defiling of a pure white woman by a lousy Indian."[32] Nevertheless, this admittedly neurotic maneuver sheds a great deal of light on the latent content of the cultural matrix "race prejudice," as well as on the manner in which marginal segments of culture may be exploited – with only a minimum of conscious guilt feelings – for the expression and implementation of socially unacceptable and highly ego-dystonic wishes and fantasies. In the same way, the aforementioned Plains Indian woman could wallow in cannibalistic fantasies simply by defining her enjoyment of these fantasies as an appreciation of tribal lore.

The assigning of newly acquired cultural items to some traditional matrix is a common occurrence in acculturated analysands. A Plains Indian analysand reported that when he went to boarding school his mother accompanied him to the bus station, singing "strong heart songs" as though he were setting out on the warpath for the first time. Such maneuvers shed a great deal of light on the dynamics of acculturation in general, and especially upon those of "antagonistic acculturation," where alien cultural *means* are borrowed in order to preserve more effectively certain indigenous *ends*.[35]

The reverse of antagonistic acculturation is represented by the attempt to fit obsolete indigenous items into the matrix of a newly adopted pattern. This process is exemplified by the transformation of indigenous deities into Christian demons, or by the destruction of native ritual objects and property in semi-Christian messianic cults, as exemplified by "cargo cults."[36] Several examples of such a reinterpretation of native cultural items by a Plains Indian analysand have been published elsewhere.[16] An anthropological analysis of the way in which the Manus detached some items of their aboriginal culture from their original matrices, and placed them in the matrices of their postwar culture, will be found in Mead's *New Lives for Old*.[37]

In a primarily anthropological paper we cannot discuss the distinctive ways in which various types of neurotics and psychotics distort, reinterpret, and totally or partially deculturalize those culture items that they use (or abuse) in connection with their personal conflicts and delusions. Nor is it necessary to do so, since this process has been described elsewhere in some detail.[27] However, we may mention, at least in passing, that the deculturalization of a cultural item in psychosis is the reverse of the process whereby a cultural matrix is assigned to an initially noncultural item.

The preceding considerations suffice to establish that no item is a part of culture unless it is assigned to a cultural matrix of meanings, values, and implications. They also underscore the multiplicity and the occasional mutual incompatibility of the several matrices to which a given item may be assigned, both by culture itself and by the individual belonging to a given culture.

These findings permit us to define culture somewhat as follows: culture is both an inner experience and a way of experiencing. Indeed, the person participating in culture does not experience it simply as something external, as something that buffets him about as a more or less patterned set of crosscurrents may do. Instead, he experiences culture as something deeply internalized, something which is an integral component of his psychic structure and psychic economy. Since this point was made with great skill and clarity by Jules Henry,[38] it seems desirable to emphasize in this context chiefly the fact that culture is a manner of experiencing the components as well as the pattern of man's world or life space. To return to the pseudoproblem of incest among apes, culture alone determines whether a nubile female is experienced as a sexual object or as a sexually taboo daughter. If the marriageable female, whom culture defines as a tabooed daughter, is, nevertheless, experienced chiefly as a sexually attractive female, neurosis and/or socially prohibited behavior is certainly imminent. Likewise, culture alone determines whether the flesh of the pig is, or is not, defined as food. On a broader level, culture alone determines whether we define mankind as a whole as fundamentally evil or whether, like the Arunta to whom a missionary tried to explain the doctrine of original sin, we reply indignantly: "All Arunta are good!" Social models determine even the manner in which we regard psychiatric problems. Accordingly, it is possible to prove that nonscientific, cultural thought models are responsible for the psychiatrist's obsession with the diagnostic value of mere adjustment, and for a great deal of "neurologizing psychiatry," or naive organicism, as well.[39] In fact, I venture to suggest that great advances in science always presuppose either major sociocultural changes or a borrowing of alien scientific knowledge *without* the cultural matrices to which such knowledge is assigned by the lending culture. This latter process is exceptionally obvious in the manner in which early Ionian, Arab, and Renaissance science came into being. The Ionians borrowed Egyptian and Babylonian temple-science, but without its religious and cultural implications. However, once their new advances were fitted into the irrational matrix[9] of Greek culture, Greek science became stultified. It was eventually borrowed by the Arabs who did not, however, take over also the matrix to which the Greeks had assigned it. In due time the progress of Arab science was halted by an integration of science with Islamic culture. Next, the men of the Renaissance borrowed arabized Greek science, but without its Islamic matrix, and made further progress until

their science, too, was forcibly co-ordinated with the more irrational aspects of occidental culture.

The cycle of matrix-free discovery – comparable to Hartmann's concept of the conflict-free sphere of the ego[40] – followed by stultification through the establishing of forced compendences between the findings of science and the irrational substratum of culture, was repeated in the age of discovery, at the beginning of the machine age, and, again, in the course of the social cataclysm that marked the onset of the atomic age. Otherwise expressed, science progresses only as long as it is not forcibly fitted into the procrustean bed of culture's irrational substratum, but declines whenever there arises the conception of, or demand for, Mohammedan, Christian, German, Marxist, or even democratic science. I imagine it is this aspect of culturally neutral science that Weston La Barre[41] had in mind when he spoke of the glorious tradition of "scientific rowdyism." Society has a right to demand that the scientist be a responsible citizen. However, once a society demands that science itself cease to be an unkempt urchin and become culturally housebroken, it automatically forfeits its scientific leadership to a society more tolerant of the basic cultural, that is, ideological neutrality of science.

While this brief sketch cannot do justice to the tremendously complex problems of the history of science, it does prove that culture is a patterned way of experiencing oneself as well as the rest of the world, and clearly specifies that the manner in which members of a given culture experience a certain item is often at variance with objective reality, as well as with the manner in which that item is experienced in another culture.

At this point we propose to advance the thesis that the full understanding of any given cultural item presupposes not only an understanding of the many discrete matrices in which it may be embedded, but also an understanding of the complex (overt and covert) relationship obtaining between the various matrices of a single trait. To take a very simple example, it is not sufficient to realize that the item "twins" has two mutually contradictory matrices in Mohave society. First and foremost, we must realize that these two matrices are conjugate, in that they implement the two poles of a fundamentally ambivalent attitude toward twins, whose birth creates serious problems even for modern families that do not lead economically marginal existences. In fact, it may be suggested that the birth of twins, precisely because it is an exceptional event, serves to crystallize a great many of the normally inhibited resentments of the parents as well as of the older siblings.

Unfortunately for the field worker, it is extremely difficult to determine every single matrix to which a given item is assigned. The position of the theoretician who, on the basis of published field reports, seeks to obtain a well-rounded understanding of the meaning of a given cultural

item, either in one culture or else in a large number of cultures, is even more difficult, since the average ethnography usually mentions only one of the matrices of a given item.

It is my belief that the field worker studying a given tribe will find it quite easy to locate the various matrices to which an item belongs if he bears in mind the variety of matrices to which that item is assigned in other cultures. The second set of Mohave beliefs concerning twins would certainly not have remained undetected for nearly half a century had field workers remembered that in other culture areas twins are openly rejected and sometimes even killed. Moreover, not even the most caninophile field worker could long remain ignorant of the secondary and wholly hostile matrix of the item "dog" in occidental culture, if he remembered that the Arab considers the dog as an unclean animal. Conversely, not even the most caninophobic student of Arab culture will remain unaware of the tremendous prestige of the greyhound in Arab society, if he remembers that the Australian native sometimes values his dingo puppy more than he values his child.

I now propose to select an extraordinarily weird item, which certainly did not diffuse from China to the South American Tupari, nor from Zoroastrian Balkh to a Greenland Eskimo village. This item is the "reversible or retractable penis." Among the Tupari[42] and the Tapirapé[43] every boy routinely learns to luxate his penis, so that, except when he is urinating or copulating, his penis is completely tucked inside his body. In South China[44] and in Indonesia[45] it is believed that the penis may retract into the abdomen with lethal results. This imaginary illness, as well as the extreme panic which it elicits, is called "koro" in Indonesia. The Mohave Indians jokingly claim that the male transvestite "pounds his penis to make it go inside and look like a vagina."[17] An Eskimo woman, who was expected to give birth to a boy, managed to persuade everyone that she had done so, but that, due to the premature intrusion of the boy's older sister, the neonate's penis retracted, turning him into a woman.[46] Legend reports that Zarathustra cured the king's favorite horse, whose legs had retracted into its body.[47] There is a scurrilous anecdote about a near-retraction of the penis in the erotic literature of eighteenth century France. Reuss[48] described the case of a German psychotic who, three times in succession, stuffed his penis down his own urethra, the way one turns a sleeve inside out. I published elsewhere the dream of a neurotic American woman, which specifically denied that the penis can retract into the body. An experienced psychoanalyst told me about a patient who wished to cover his entire body with a rubber sheathing; the portion covering the penis could then be inverted, so as to resemble a vagina. Another competent analyst reports that a neurotic adolescent was afraid that his penis might retract into his abdomen, turning his urethra into a uterus.

It is my considered opinion that no real understanding of the idea of

the reversible penis is possible unless one takes into account all of the matrices to which it is assigned in various cultures, including traditional costume, dangerous illness, tribal humor, socially accepted lie, magical cure, erotic anecdote, psychotic behavior, neurotic fantasy, and neurotic denial.

I fully realize that this position represents an endorsement of the nowadays despised "comparative method." The fact remains that the comparative method was extremely productive of important anthropological insights. Its sole drawback was that the method itself was never properly justified. I now propose to offer a systematic justification of that technique.

I take as my point of departure the mathematician's ergodic hypothesis that postulates that the results of a million consecutive tosses of a coin are the same as the results of the simultaneous tossing of a million identical coins. This hypothesis is generally accepted as valid, even though mathematicians differ as to whether the ergodic hypothesis has ever been actually proved.

It is my thesis that a complete exploration of the meanings, values, and connotations of a given item by psychoanalyzing a single individual, or the complete anthropological exploration of all matrices to which that item belongs in a given culture, or a reasonably complete survey of the *primary* matrices to which this item is assigned in a large number of cultures will all yield exactly the same insights into the real meaning of that item. In concrete terms, I believe that, had I been able to analyze every single ramification of the dream in which my analysand denied the possibility that the penis can retract into the abdomen, I should have obtained subjective equivalents of every known cultural context of this belief. I am equally convinced that an exhaustive study of all ramifications of the "koro" pattern in Java would yield the complete range of data pertaining to the retractible penis in other cultures. Conversely, a list of the forms in which this idea is expressed in a large number of different cultures is, at the same time, also a catalogue of the matrices in which this idea may appear in a given culture. Moreover, it corresponds to an inventory of the individual connotations that an analysand may, on various conscious or unconscious levels, assign to this idea.

Needless to say, this thesis is hard to prove. There is, however, extremely telling factual evidence that can be mustered in support of this view and that I now propose to discuss in some detail:

(1) A survey of data on abortion in 400 primitive cultures did not disclose even a single custom, idea, or attitude that analysts have failed to find in occidental women who had aborted, or wished to abort, or who had abortion fantasies.

(2) On the basis of the Mohave belief that if a woman violates a certain pregnancy taboo she will miscarry, I inferred[50] that there must

exist at least one tribe in which women deliberately violate certain pregnancy taboos in order to abort. One year later, after surveying an additional one hundred groups, I discovered precisely this predicted practice among the Maori.[51]

(3) On the basis of predominantly African data I concluded that the illegitimate child is often fantasied to be the offspring of the girl's father. My book[34] was already in galley proof when, in connection with another investigation, I encountered this very belief among the African Fan.[52]

(4) A Sedang girl, who was impregnated and aborted by her father, pretended that she bled because she was bitten by leeches, which are used as a means of procuring abortions in Persia.[34]

(5) An Aleut abortionist refused to discuss her practices and instead chose to discuss – of all things – baskets. It is hardly necessary to point out that baskets and other containers are well-known symbols of the female genitalia, and especially of the uterus.[34]

I am therefore led to conclude that the uniformity of the human psyche implies also the uniformity of human Culture with a capital C. As with individuals, cultures differ from each other chiefly in the manner in which the constituent items are juxtaposed and arranged into patterns. They also differ in terms of the fact that the *primary* matrix of a certain item in one culture may be a secondary matrix, or else the latent content of that trait, in another culture; the reverse, of course, also holds true. In fact, the systematic affirmation of one belief necessarily implies the denial of the opposite belief, and this denial is quite as much a constituent element of that culture as is the affirmation itself. Thus, the unqualified affirmation of absolute monotheism in Islam indicates the presence of (rejected) polytheistic ideas. A psychoanalytic analogy may clarify the import of this statement:

A certain person dreamed that three fish, named Matthew, Mark, and Luke, were swimming in a fishbowl. An analysis of this dream disclosed that the real subject of the dream was *John*, whose name was ostentatiously omitted from the dream.[53]

On the basis of the preceding considerations we are now able to formulate the precise nature of the nexus between culture and the human mind.

(1) Historically, culture and the human mind are co-emergents and presuppose each other.

(2) Attempts to derive culture genetically from the nature of the human psyche are quite as meaningless as attempts to derive the human psyche genetically from culture.

(3) The acquisition of Culture *per se* (as distinct from *Eskimo* or *Hottentot* culture) by the infant, and its transformation from an immature specimen of the (zoological) *genus homo* into a human being occur simultaneously. This functionally indivisible dual process may be

designated by the term "humanization" and must be differentiated from the acquisition of a *specific* culture, which may be called "ethnicization." For example, in learning to *speak* the child becomes human; in learning to speak *Sioux* it becomes a certain kind of Plains Indian. Humanization through the acquisition of Culture actualizes the human being's potentialities; ethnicization simply provides one set of specific means for their actualization.[53]

(4) The anthropologist can use only a psychological system whose focus is not *genus homo* (defined zoologically), but *zoön politikon* – the creature which lives in a culturally organized community and not in a biologically organized herd or beehive. Only psychoanalysis satisfies this criterion; no sound anthropology is possible without it.

(5) The psychoanalyst can use only a science of man that studies his distinctively and uniquely human behavior. Only anthropology satisfies this criterion; no sound psychoanalysis is possible without it.

(6) Psychoanalysis and anthropology alike must take cognizance of man's characteristics that are nonspecific, being shared with other, cultureless, beings that have no human psyche. In other words, man's biological nature must be taken into account by both the anthropologist and the psychoanalyst. However, it must be viewed not as a true *causa causans* of culture and the human psyche, but solely as the terrain on which culture and the human mind may develop, as the raw material with which culture and the human mind operate, and as an internal limitation of the theoretically almost unlimited variability of culture and of the mind. Those traits that man shares with other primates can no more explain his psyche and culture than the nature of iron can explain the structure and function of a chronometer. Any science of man that refuses to recognize this fact is not science, but science fiction.

(7) Psychoanalysis and anthropology must hang together, lest they hang separately in an age of automation and electric brains, an age that has returned to the philosophy of Roman slave keepers, and has extended the concept of the slave as a kind of machine to mankind as a whole. A new science, combining psychoanalysis and anthropology, is the last bulwark of the concept of man as an end in himself.

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CONFERENCE HELD

SECTION OF BIOLOGY

THE EFFECTS OF THE SULFONYLUREAS AND RELATED COMPOUNDS IN EXPERIMENTAL AND CLINICAL DIABETES

Thursday, February 14 and
Friday, February 15, 1957

Conference Chairman: Rachmiel Levine
Michael Reese Hospital, Chicago, Ill.

THURSDAY, FEBRUARY 14, 1957

Session Chairman: Rachmiel Levine
Michael Reese Hospital, Chicago, Ill.

9:00 A.M. –
Greetings from the Academy – A. S. Gordon, Chairman, Section of Biology, The New York Academy of Sciences, New York, N. Y.; New York University, New York, N. Y.

Introduction – Rachmiel Levine, Michael Reese Hospital, Chicago, Ill.

"The Development of Our Knowledge Concerning the Hypoglycemic Sulfonamides between 1942 and 1955" – A. L. Loubatières, Faculté de Médecine de Montpellier, Institut de Biologie, Montpellier, France.

"Action of the Hypoglycemic Sulfonamides in Experimental Animals Subjected to Various Endocrine Conditions" – Bernardo A. Houssay, Instituto de Biologia y Medicina Experimental, Buenos Aires, Argentina.

Discussion

"The Effect of Sulfonylureas on the Peripheral Utilization of Carbohydrates in Animals" – Arne N. Wick, Scripps Clinic and Research Foundation, La Jolla, Calif.

"Peripheral and Hepatic Actions of Tolbutamide" – H. Elrick and R. Purnell, Radioisotope Service and Medical Research Laboratory, Veterans Administration Hospital, Denver, Colo.

"The Effect of Sulfonylureas on the Peripheral Utilization of Carbohydrates in Man" – F. C. Goetz, University of Minnesota Medical School, Minneapolis, Minn.

"Intermediary Metabolites in Peripheral and Hepatic Vein Blood Following Intravenous Tolbutamide in Normal and Diabetic Humans" – Max

Miller, J. W. Craig, M. Mackenzie, W. R. Drucker, and M. Cammarn, Western Reserve University, Lakeside Hospital, Cleveland, Ohio.

Discussion

Session Chairman: Bernardo A. Houssay
Instituto de Biologia y Medicina Experimental
Buenos Aires, Argentina

2:00 P.M. –

"Studies on the Site of Action of Sulfonylureas in Man" – Albert E. Renold, I. A. Winegrad, B. R. Boshell, and G. W. Thorn, Peter Bent Brigham Hospital, Boston, Mass.

"Effects of Carbutamide and Tolbutamide on the Disposition of Glucose and of Pentoses in Man" – T. F. Frawley and S. Segal, Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

"Effects of Tolbutamide on the Metabolism of Fructose and Glucose" – John Moorhouse, Robert M. Kark, and D. D. Gelman, University of Illinois College of Medicine, Chicago, Ill.

Discussion

"The Sulfonylureas and Insulinase Activity" – I. A. Mirsky, University of Pittsburgh School of Medicine, Pittsburgh, Pa.

"*In Vitro* Studies on the Effects of the Sulfonylureas on Liver" – Martha Vaughan, National Heart Institute, National Institutes of Health, Bethesda, Md.

Discussion

"Studies on the Absorption, Mechanism of Action, and Excretion of Tolbutamide in the Rat" – W. L. Miller, Jr., The Upjohn Co., Kalamazoo, Mich.

"Perfusion Studies with Sulfonylureas in Dogs" – A. R. Colwell, Jr., J. A. Colwell, and A. R. Colwell, Sr., Northwestern University School of Medicine, Chicago, Ill.

"Studies on the Disposition of Isotopic Glucose *in Vivo* and *in Vitro* under the Influence of Sulfonylureas" – J. Ashmore, G. F. Cahill, Jr., and Earl A. Scott, Harvard University Medical School, Boston, Mass.

Discussion

FRIDAY, FEBRUARY 15, 1957

Session Chairman: Arthur R. Colwell, Sr.
Northwestern University School of Medicine
Chicago, Ill.

9:00 A.M. –

"Functional and Histological Studies Concerning the Action of Sulfonylureas" – B. W. Volk, M. G. Goldner, S. Weisenfeld, and S. S. Lazarus, Isaac Albert Research Institute of the Jewish Chronic Disease Hospital, Brooklyn, N. Y.

"Sex Differences in the Extractable Insulin Content of Human Diabetics" – G. W. Wrenshall, Banting and Best Institute, University of Toronto, Toronto, Ont., Canada.

Discussion

"Report on Studies Done at the Best Institute, University of Toronto" – G. W. Wrenshall, Banting and Best Institute, University of Toronto, Toronto, Ont., Canada.

"Long-Term Studies of the Sulfonylureas in Totally Depancreatized Dogs" – Henry T. Ricketts and H. L. Wildberger, University of Chicago, Billings Hospital, Chicago, Ill.

"Studies concerning the Role of the Liver in the Hypoglycemic Response of Animals to Tolbutamide" – W. E. Dulin, The Upjohn Co., Kalamazoo, Mich.

Discussion

"On the Mechanism of Action of the Hypoglycemic Sulfonamide Derivatives" – A. L. Loubatières, Faculté de Médecine de Montpellier, Institut de Biologie, Montpellier, France.

Discussion

Session Chairman: Alexander Marble
Joslin Clinic, Boston, Mass.

2:00 P.M. –

"Metabolic Effects of Sulfonylureas in Normal Man and in Various Types of Diabetic Patients" – S. S. Fajans, University of Michigan, University Hospital, Ann Arbor, Mich.

"Effects of Tolbutamide on the Diabetes of Acromegaly, and on the Blood Sugar in Patients with Altered Endocrine States" – D. M. Bergenstal, H. Lubs, L. Hallman, and J. Schricker, Endocrinology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Md.

"Clinical Experiences with the Sulfonylureas in Diabetes Mellitus" – G. G. Duncan, Jefferson Medical College, Pennsylvania Hospital, Philadelphia, Pa.

Discussion

"Clinical Experience with Sulfonylurea Compounds in Diabetes" – Alexander Marble and R. Camerini-Davalos, Joslin Clinic, Boston, Mass.

"The Use of Tolbutamide in the Management of Adult Diabetes" – S. Sherry, The Jewish Hospital of St. Louis, St. Louis, Mo.

"Use of the Sulfonylureas in Diabetes Mellitus" – S. J. N. Sugar, Kaywood Gardens, Mt. Rainier, Md.

Discussion

"Further Experience with the Use of Sulfonylureas in Diabetes" – Samuel B. Beaser, Bay State Road, Boston, Mass.

"Thyroid Function of Diabetic Patients as Influenced by the Sulfonylureas" – Thomas H. McGavack, New York Medical College, Flower and Fifth Avenue Hospital, New York, N. Y.

"Experience with the Sulfonylurea Management of 500 Cases of Diabetes on an Ambulatory Basis" – Henry H. Dolger, The Mt. Sinai Hospital, New York, N. Y.

Discussion

Concluding Remarks – Rachmiel Levine, Michael Reese Hospital, Chicago, Ill.

NEW MEMBERS

Elected February 28, 1957

CORPORATION MEMBERSHIP

National Drug Co., Philadelphia, Pa.
Wallace Laboratories, New Brunswick, N.J.

SUSTAINING MEMBERSHIP

McLeod, Christie E., M.D., Pathology. Pathologist, Middlesex Memorial Hospital, Middletown, Conn.
Meyer, Robert John, Ph.D., Organic Analytical Chemistry. Research Associate, University of Wisconsin, Madison, Wis.
Pepi, John Francis, M.D., Cancer. Medical Director, Penal Institutions, Suffolk County, East Boston, Mass.
Pinotti, Mario, M.D., Biology. Director, Department Nacional de Endemias Rurais, Rio De Janeiro, Brazil.
Reed, Ernest, Ph.D., Microbiology & Biochemistry. Director, Syracuse University Research Institute, Syracuse, N.Y.
Schmitz, Fred, Pharmaceuticals. Senior Partner, Schmitz-Schoenewaldt-Turner Co., New York, N.Y.
Sears, Robert A., M.D., Neurosurgery. Private Practice, Atlanta, Ga.
Skillman, Edward, M.S., Engineering. Designing Engineer, Enterprise, Kans.
Stoll, Georges, M.D., Surgery. Surgeon, Haguenau, France.
Thornton, Madeline J., M.D., Medicine. Associate Professor, University of Wisconsin, Madison, Wis.

ACTIVE MEMBERSHIP

Abrams, Richard, Ph.D., Biochemistry. Associate Director, Montefiore Hospital, Pittsburgh, Pa.
Adams, Eugene V., M.S., Virology. Virologist, E.R. Squibb & Co., Highland Park, N.J.
Aqvist, Stig E.G., M.D., Biochemistry. Rockefeller Fellow, National Institutes of Health, Bethesda, Md.
Amromin, George David, M.D., Pathology. Pathologist in Chief, City of Hope Medical Center, Duarte, Calif.
Antoniades, Harry Nicolas, Ph.D., Protein Chemistry. Research Associate, Harvard University Medical School, Boston, Mass.
Aronson, Willard, M.D., Pathology. Resident, Pathology, Philadelphia General Hospital, Philadelphia, Pa.
Bachman, Leonard, M.D., Medicine. Directory Division, Hospital of Philadelphia, Philadelphia, Pa.
Ball, Milton H., General Science. President, Inter City Paper Co., Long Beach, L.I., N.Y.
Bauer, Goran C.H., M.D., Calcium Metabolism. Associate Professor, University of Lund, Lund, Sweden.
Bauer, Heinz, M.D., Pathology. Assistant Professor, Emory University, Decatur, Ga.
Berman, Edgar F., M.D., Prosthetics. Surgeon, The Johns Hopkins Hospital, Baltimore, Md.
Blackburn, Charles Ruthven Bickerton, M.D., Medicine. Professor, Medicine, University of Sidney, Sidney, Australia.
Boonstra, Charles E., M.D., Medicine. Pathologist, Caylor-Nickel Clinic, Bluffton, Ind.
Brown, David Reid, M.D., Medicine. Supervising Physician, J.N. Adam Memorial Hospital, Perrysburg, N.Y.
Cardenas, Nicholas, M.D., Pediatrics. Resident, St. Christopher's Hospital for Children, Philadelphia, Pa.

Carlsson, Arvid, M.D., Biochemistry. Associate Professor, Pharmacology, University of Lund, Lund, Sweden.
Cassano, Francesco, Ph.D., Medicine. Director, Ospedale Clivile, Lucca, Italy.
Chan, Wallace Lane, M.D., Medical Physiology. Assistant, George Washington University, Washington, D.C.
Chang, Norman H.C., B.A., Cancer Cytology. Senior Laboratory Technician, Granada Hills, Calif.
Chattalas, Angelos Mike, M.D., Chemical Education. Head, Science Department, Cherry Lawn School, New York, N.Y.
Childs, Wesley A., M.D., Tissue Transplantation. Chief, Surgical Service, Veterans Administration, Albuquerque, N. Mex.
Chiossone, Edgar, M.D., Biology. Resident, Otolaryngology Department, New York University, Bellevue Medical Center, New York, N.Y.
Clewe, Thomas H., M.D., Physiology. Research, Department of Anatomy, Yale University Medical School, New Haven, Conn.
Cohen, Sophia M., B.S., Virology. Associate Bacteriologist, New York State Department of Health, Albany, N.Y.
Contopoulos, Alexander N., Ph.D., Biology. Acting Assistant Professor, Anatomy, University of California, Berkeley, Calif.
Coon, William Warner, M.D., Biology. Instructor, Surgery, University of Michigan, Ann Arbor, Mich.
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Dienstag, Leo Nathan, M.D., Medicine. Senior Resident, Veterans Administration Hospital, New York, N.Y.
Diercks, Fred H., M.S., Microbiology. Captain, U.S. Army, Pittsburgh, Pa.
Duffy, Regina M., Ph.D., Botany. Assistant Professor, New Jersey State Teachers College, Jersey City, N.J.
Dulaney, Eugene L., Ph.D., Mycology. Senior Microbiologist, Merck Sharpe & Dohme, Rahway, N.J.
Feinberg, Elliot, D.D.S., Dentistry. Private Practice, Scarsdale, N.Y.
Findlay, Charles Walter, Jr., M.D., General Surgery. Assistant Attending Surgeon, Presbyterian Hospital, New York, N.Y.
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Frank, Mary Elizabeth, M.D., Internal Medicine. Staff, Doylestown Hospital, Doylestown, Pa.
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Freygang, Walter H., Jr., M.D., Neurophysiology. Surgeon, Public Health Service Commissioned Corps, Bethesda, Md.
Garcia, Eve Otalora, M.D., Biology. Chief, Department of Bacteriology, Instituto Nacional de Neumologia, San Angel, D.F., Mexico.
Gatling, Robert R., M.D., Connective Tissue. Pathologist, Lewis-Gale Hospital, Roanoke, Va.
Gaumer, Albert E.H., Ph.D., Anatomy. Associate Professor, Moravian College, Bethlehem, Pa.
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Gsell, Otto R., Dr. Med., Internal Medicine. Director, Medizinische Universitäts-Poliklinik, Basel, Switzerland.

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Miller, James Stephen, A.B., Psychology. Student, Stanford University, Stanford, Calif,
Miller, John C., Ph.D., Rheology of High Polymers. Research Chemist, Bakelite Company, Bound Brook, N.J.
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Moore, Floy Edward, Ph.D., Organic Reagents. Assistant Professor, Loyola University, Chicago, Ill.
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Prevost, Gustave, Ph.D., Freshwater Fisheries. Director, Biological Bureau, Université de Montreal, Montreal, P.Q., Canada.
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Sapirstein, Leo A., M.D., Physiology. Professor, Ohio State University, Columbus, Ohio.
Schick, Armin F., M.D., Internal Medicine. Assistant Clinical Professor, University of Illinois, Chicago, Ill.
Schipper, I.A., D.V.M., Veterinary Science. Assistant Professor, North Dakota Agricultural College, Fargo, N.Dak.
Schlack, Carl August, D.D.S., Oral Biology. Director, U.S. Naval Training Center, San Diego, Calif.
Schlesinger, R. Walter, M.D., Virology. Director, Department of Microbiology, St. Louis University, St. Louis, Mo.
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Seegers, Walter Henry, Ph.D., Physiology. Associate Professor, Wayne State University, Detroit, Mich.
Seidenstein, Howard R., M.D., Medicine. Private Practice, New Rochelle, N.Y.
Selzer, Arthur, M.D., Physiology. Associate Clinical Professor, Stanford University, Stanford, Calif.
Serio, Joseph, D.D.S., Radiology. Private Practice, Woodhaven, N.Y.
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Shoemaker, William C., M.D., Biology. Research Fellow, Harvard University, Cambridge, Mass.
Siegel, Irving H., Ph.D., Mathematics. Consultant, George Washington University, Washington, D.C.
Silver, Melvin J., D.Sc., Lipide Anticoagulants. Research Biochemist, Jefferson Medical College, Philadelphia, Pa.
Silverman, Frederic N., M.D., Pediatric Radiology. Associate Professor, Pediatrics, University of Cincinnati, Cincinnati, Ohio.
Siminovitch, David, Ph.D., Plant Physiology. Chemist, Science Service, Dominion Experimental Farm, Ottowa, Ont., Canada.
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